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<p>(21) International Application Number: PCT/US99/13948</p> <p>(22) International Filing Date: 18 June 1999 (18.06.99)</p> <p>(30) Priority Data: 60/093,639 21 July 1998 (21.07.98) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).</p> <p>(72) Inventor; and (75) Inventor/Applicant (<i>for US only</i>): BOCAN, Thomas, Michael, Andrew [US/US]; 5588 Lakeshore Drive, Ann Arbor, MI 48108 (US).</p> <p>(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.</p>	<p>(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>	
(54) Title: COADMINISTRATION OF ACAT AND MMP INHIBITORS FOR THE TREATMENT OF ATHEROSCLEROTIC LESIONS		
<p>(57) Abstract</p> <p>This invention is the coadministration of ACAT and MMP inhibitors for the reduction of both the macrophage and smooth muscle cell component of atherosclerotic lesions, thus impairing the expansion of existing lesions and the development of new lesions and for the prevention of plaque rupture and the promotion of lesion regression in a mammal.</p>		

COADMINISTRATION OF ACAT AND MMP INHIBITORS FOR THE
TREATMENT OF ATHEROSCLEROTIC LESIONS

BACKGROUND OF THE INVENTION

Enzymes known as native matrix metalloproteinases (MMP) are classes of
5 naturally occurring enzymes found in most mammals. They are zinc proteases that
hydrolyze collagens, proteoglycans, and glycoproteins. The classes include
gelatinase A and B, stromelysin-1 and -2, fibroblast collagenase, neutrophil
collagenase, matrilysin, metalloelastase, and interstitial collagenase. These
10 enzymes are implicated in a number of diseases which result from breakdown of
connective tissues, such as rheumatoid arthritis, osteoarthritis, osteoporosis,
multiple sclerosis, and even tumor metastasis. The expression of MMPs in
atherosclerosis is discussed in White A., Bocan T.M.A., Boxer P.A., Peterson J.T.,
Schrier D. Emerging therapeutic advances for the development of second
15 generation matrix metalloproteinase inhibitors. *Curr. Pharm. Design*
3:45-58 (1997). To date, inhibitors of matrix metalloproteinases have not been
utilized with ACAT inhibitors.

United States Patent Application 08/987167 filed December 8, 1997,
teaches MMP inhibitors and their preparation and is hereby incorporated by
reference.

20 Compounds which inhibit acyl-coenzyme A:cholesterol acyltransferase are
known as ACAT inhibitors. Certain ACAT inhibitors and the methods for
preparing them are taught in United States Patent 5,491,172 and its divisional
5,633,287 which are hereby incorporated by reference.

United States Patent 5,756,545 covers MMP inhibitors especially
25 2-(4'-Bromo-biphenyl-4-sulfonylamino)-3-methyl-butyric acid. This patent is
hereby incorporated by reference.

United States Patent 5,441,975 teaches ACAT inhibitors, especially
N-(2,6-Diisopropyl-phenyl)-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide.
This and other patents in the same patent family: 5,646,170; 5,693,657; and
30 5,366,987 are hereby incorporated by reference.

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The invention is further a method for preventing plaque rupture and for promoting lesion regression by administering a combination of an ACAT inhibitor and an MMP inhibitor.

5 The method is practiced by administering a chemical compound effective in inhibiting the biological activity of a matrix metalloproteinase such as collagenase, stromelysin, gelatinase, or elastase. The numerous compounds known to be matrix metalloproteinase inhibitors are useful in the practice of this invention.

10 The method is practiced by administering a chemical compound which inhibits the enzyme acyl-coenzyme A:cholesterol acyltransferase. The numerous compounds known as ACAT inhibitors are useful in the practice of this invention.

A "matrix metalloproteinase inhibitor" as used herein is any chemical compound that inhibits by at least five percent the hydrolytic activity of at least one matrix metalloproteinase enzyme that is naturally occurring in a mammal. 15 Such compounds are also referred to as "MMP inhibitors." Numerous matrix metalloproteinase inhibitors are known, and all are useful in the method of this invention. For example, 4-biarylbutyric and 5-biarylpentanoic acid derivatives are described in United States Patent Application 339846 filed November 15, 1994, which is incorporated herein by reference. The compounds are defined generally 20 as (T)_xA-B-D-E-G. Over 400 specific compounds are named, and each is incorporated herein and can be employed in this invention. Especially preferred compounds to be utilized include the following:

[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -(2-methylpropyl)- γ -oxo-;
[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -(2-methylpropyl)- γ -oxo-,
25 (S)-;
[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -(2-methylpropyl)- γ -oxo-,
(R)-;
[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- β -(2-methylpropyl)- γ -oxo-, (S);
[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- β -(2-methylpropyl)- γ -oxo-,
30 (R)-;
[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- γ -oxo-;
[1,1'-Biphenyl]-4-butanoic acid, 4'-bromo- γ -oxo-;

- [1,1'-Biphenyl]-4-butanoic acid, 3',4'-dichloro- γ -oxo- α -(3-phenylpropyl)-;
 [1,1'-Biphenyl]-4-butanoic acid, 3',5'-dichloro- γ -oxo- α -(3-phenylpropyl)-;
 [1,1'-Biphenyl]-4-butanoic acid, 4'-(acetyloxy)- γ -oxo- α -(3-phenylpropyl)-;
- 5 Benzenepentanoic acid, α -[2-[4-(5-chloro-2-thienyl)phenyl]-2-oxoethyl]-;
 2-Furancarboxylic acid, 5-[4-(3-carboxy-1-oxo-6-phenylhexyl)phenyl]-;
 Benzenepentanoic acid, α -[2-oxo-2-[4-(3-pyridinyl)phenyl]ethyl]-;
 Benzenepentanoic acid, α -[2-oxo-2-[4-[6-(pentyloxy)-3-pyridinyl]-phenyl]ethyl]-;
- 10 [1,1'-Biphenyl]-4-butanoic acid, γ -oxo-4'-(pentylothio)- α -(3-phenylpropyl);
 [1,1'-Biphenyl]-4-butanoic acid, 4'-methoxy- γ -oxo- α -(3-phenylpropyl)-;
 [1,1'-Biphenyl]-4-butanoic acid, 3'-chloro-4'-fluoro- γ -oxo- α -(3-phenylpropyl)-;
- 15 [1,1'-Biphenyl]-4-butanoic acid, 4'-ethoxy- γ -oxo- α -(3-phenylpropyl)-;
 Benzenepentanoic acid, α -[2-oxo-2-[4-(3-thienyl)phenyl]ethyl]-;
 [1,1'-Biphenyl]-4-butanoic acid, 2',4'-dichloro- γ -oxo- α -(3-phenylpropyl)-;
 [1,1'-Biphenyl]-4-butanoic acid, 4'-formyl- γ -oxo- α -(3-phenylpropyl)-;
 [1,1'-Biphenyl]-4-butanoic acid, γ -oxo- α -(3-phenylpropyl)-3',5'-
- 20 bis(trifluoromethyl)-;
 Benzenepentanoic acid, α -[2-oxo-2-[4-(2-thienyl)phenyl]ethyl]-;
 [1,1'-Biphenyl]-4-butanoic acid, γ -oxo- α -(3-phenylpropyl)-3'-(trifluoromethyl)-;
- 25 [1,1'-Biphenyl]-4-butanoic acid, 2'-formyl- γ -oxo- α -(3-phenylpropyl)-;
 [1,1'-Biphenyl]-4-butanoic acid, 4-hydroxy- γ -oxo- α -(3-phenylpropyl)-;
 [1,1'-Biphenyl]-4-butanoic acid, γ -oxo- α -(3-phenylpropyl)-4'-propoxy-;
 [1,1'-Biphenyl]-4-butanoic acid, γ -oxo-4'-(pentyloxy)- α -(3-phenylpropyl)-;
- 30 [1,1'-Biphenyl]-4-butanoic acid, γ -oxo-4'-(pentyloxy)- α -(3-phenylpropyl)-, (S)-;

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- [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- γ -oxo- α -[(trimethylsilyl)-methyl]-;
- [1,1'-Biphenyl]-4-butanoic acid, 4'-bromo- γ -oxo- α -(3-phenylpropyl)-;
- [1,1'-Biphenyl]-4-butanoic acid, γ -oxo- α -(3-phenylpropyl)-;
- 5 [1,1'-Biphenyl]-4-butanoic acid, 4'-amino- γ -oxo- α -(2-phenylethyl)-;
- [1,1'-Biphenyl]-4-butanoic acid, γ -oxo- α -(2-phenylethyl)-4'-
- [(phenylmethoxy)carbonyl]amino)-;
- [1,1'-Biphenyl]-4-butanoic acid, 4'-[[1,1-dimethylethoxy)-carbonyl]amino]- γ -oxo- α -(2-phenylethyl)-;
- 10 [1,1'-Biphenyl]-4-butanoic acid, 4'-(acetylamino) γ -oxo- α -(2-phenylethyl)-;
- [1,1'-Biphenyl]-4-butanoic acid, γ -oxo-4'-[(1-oxopentyl)amino]- α -(2-phenylethyl)-;
- [1,1'-Biphenyl]-4-butanoic acid, 4'-[(3,3-dimethyl-1-oxobutyl)amino]- γ -oxo- α -(2-phenylethyl)-;
- 15 [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[2-[2-(methoxycarbonyl)-phenyl]ethyl]- γ -oxo-;
- [1,1'-Biphenyl]-4-butanoic acid, α -[2-(2-carboxyphenyl)ethyl]-4'-chloro- γ -oxo-;
- 20 [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[2-[2-[(diethylamino)-carbonyl]phenyl]ethyl]- γ -oxo-;
- [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[2-[3-[(diethylamino)carbonyl]phenyl]ethyl]- γ -oxo-, (*S*)-;
- [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[2-[3-[(diethylamino)carbonyl]phenyl]ethyl]- γ -oxo-, (*R*)-;
- 25 Cyclopentanecarboxylic acid, 2-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-5-[(phenylmethoxy)methyl]-, (1 α ,2 β ,5 β)-;
- Cyclopentanecarboxylic acid, 2-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-5-(phenoxymethyl)-, (1 α ,2 β ,5 β)-;
- 30 Cyclopentanecarboxylic acid, 2-[(benzoyloxy)-methyl]-5-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-, (1 α ,2 β ,5 β)-;

Benzoic acid, 4-methoxy-, [2-carboxy-3-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl ester, (1 α ,2 β ,3 α)-;

Cyclopentanecarboxylic acid, 2-[(2-benzoxazolylthio)methyl]-5-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-, (1 α ,2 β ,5 β)-;

5 Cyclopentanecarboxylic acid, 2-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-5-[(1,3-dihydro-4-nitro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-, (1 α ,2 β ,5 β)-;

Cyclopentanecarboxylic acid, 2-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-5-[(1,3-dihydro-5-nitro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-, (1 α ,2 β ,5 β)-;

10 2*H*-Benz[*f*]isoindole-2-butanoic acid, α -[2-(4'-ethoxy[1,1'-biphenyl]-4-yl)-2-oxoethyl]-1,3-dihydro-1,3-dioxo-;

[1,1'-Biphenyl]-4-butanoic acid, α -(acetylamino)-4'-chloro- γ -oxo-;

2*H*-Isoindole-2-hexanoic acid, α -[2-(4'-chloro[1,1'-biphenyl]-4-yl)-2-oxoethyl]-1,3-dihydro-1,3-dioxo-;

15 [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[[[3-(methoxycarbonyl)-phenyl]thio]methyl]- γ -oxo-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[[[2,6-(dimethylphenyl)-thio]methyl]- γ -oxo-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[[[4-fluoro-2-(methoxycarbonyl)phenyl]thio]methyl]- γ -oxo-;

20 [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[[[3-[(diethylamino)-carbonyl]phenyl]thio]methyl]- γ -oxo-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[[[2-[(dimethylamino)-carbonyl]phenyl]thio]methyl]- γ -oxo-;

25 [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[[[3-[(dimethylamino)-carbonyl]phenyl]thio]methyl]- γ -oxo-;

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, 3-[(4'-(pentyloxy)[1,1'-biphenyl]-4-yl)carbonyl]-, (2-*endo*,3-*exo*)-;

1-Cyclopentene-1-carboxylic acid, 5-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-;

30 Cyclopentanecarboxylic acid, 2-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-5-[(phenylmethyl)thio]-, (1 α ,2 β ,5 α)-;

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[1,1'-Biphenyl]-4-butanoic acid, α -[2-(3-iodophenyl)ethyl]- γ -oxo-4'-(pentyloxy)-;

[1,1'-Biphenyl]-4-butanoic acid, α -[2-(3-iodophenyl)ethyl]- γ -oxo-4'-(phenylmethoxy)-;

5 [1,1'-Biphenyl]-4-butanoic acid, α -[2-(3-[(diethylamino)carbonyl]-phenyl)ethyl]- γ -oxo-4'-(pentyloxy)-;

[1,1'-Biphenyl]-4-butanoic acid, α -[2-(3-[(diethylamino)carbonyl]-phenyl)ethyl]- γ -oxo-4'-(phenylmethoxy)-;

10 1,2-Pyrrolidinedicarboxylic acid, 3-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-, 1-(phenylmethyl) ester, (2*S-trans*)-;

1,2-Pyrrolidinedicarboxylic acid, 3-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-, 1-(phenylmethyl) ester, (2'*R-trans*)-;

L-Proline, 3-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1-[(phenylmethyl)amino]carbonyl]-, *trans*-;

15 L-Proline, 3-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1-(1-oxo-3-phenylpropyl)-, *trans*-;

L-Proline, 3-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1-(phenylacetyl)-, *trans*-;

20 L-Proline, 3-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1-(3,3-dimethyl-1-oxobutyl)-, *trans*-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -heptyl- γ -oxo-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -decyl- γ -oxo-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-nitro- γ -oxo- α -(2-phenylethyl)-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-cyano- γ -oxo- α -(2-phenylethyl)-;

25 [1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[2-(2-iodophenyl)ethyl]- γ -oxo-;

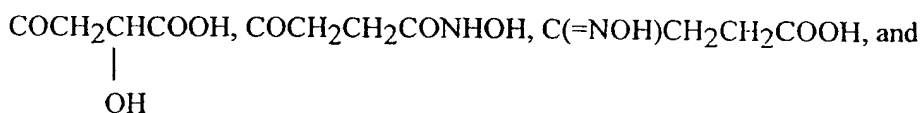
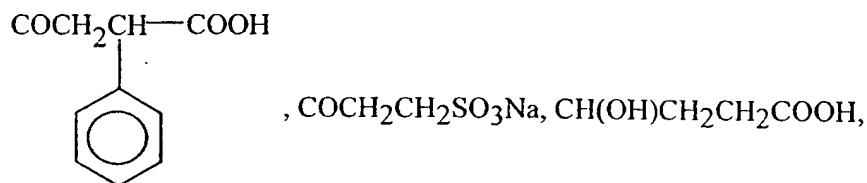
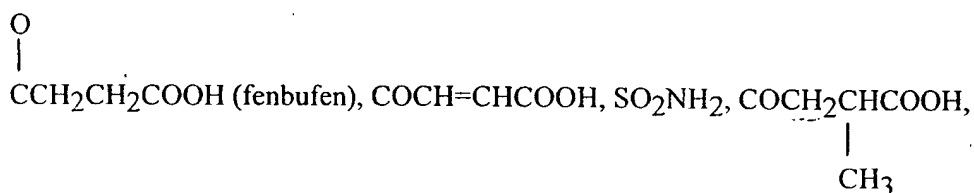
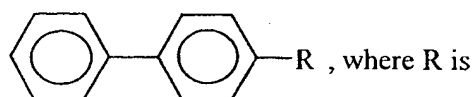
[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[2-(3-iodophenyl)ethyl]- γ -oxo-;

[1,1'-Biphenyl]-4-butanoic acid, 4'-chloro- α -[2-(4-iodophenyl)ethyl]- γ -oxo-;

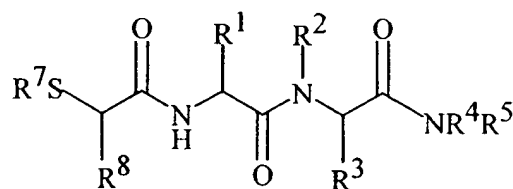
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Fenbufen and compounds related to fenbufen can be utilized. Such compounds are described in United States Patent Number 3,784,701 and by Child, et al., *J. Pharm. Sci.*, 1977;66:466-476, and *Arzneim-Forsch*, 1980;30(4A):695-702, all of which are incorporated herein by reference. Preferred compounds from the fenbufen series to be utilized in this invention have the formula



Numerous peptides are known matrix metalloproteinase inhibitors. Typical of such peptides are those described in United States Patent Number 5,300,501; 5,530,128; 5,455,258; 5,552,419; WO 95/13289; and WO 96/11209, all of which are incorporated herein by reference. Such compounds are illustrated by the formula



where each of the variable groups can include hydrogen alkyl, aryl, heteroaryl, alkenyl, alkynyl, carboxy, and the like. Preferred compounds from within this class which can be utilized in the method of this invention include the following:

25

N-[2-Acetylmercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanyol]-L-valinyl-L-phenylalanine N-methylamide;

5 N-[2-Acetylmercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-tryptophan N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

10 N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-valinyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-tryptophan N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-[β -(4-thiazolyl)]alanine N-methylamide;

15 N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-(β -(2-pyridyl))alanine N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-5-methyl-L-glutamicacid N-methylamide;

20 N-[2-Acetylmercapto-6-phthalimidohexanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-2-(3-phthalimido) phenylacetyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-5-methoxycarbonylpentanoyl]-L-phenylalanine N-methylamide;

25 N-[2-Mercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-trptophan N-methylamide;

30 N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-L-tryptophan N-methylamide;

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- N-[N-(Mercaptoacetyl)-L-threonyl]-L-phenylalanine methylamide;
N-[N-(Mercaptoacetyl)-L-leucyl]-L-tryptophan methylamide;
[4-(N-Hydroxyamino)-2(R)-cyclohexylmethylsuccinyl]-L-β-
cyclohexylalanine-N-(2-phenylethyl)amide;
- 5 [4-N-(Hydroxyamino)-2R-isobutylsuccinyl]-L-β-cyclohexylalanine-N-
(2-phenylethyl)amide;
 [4-(N-hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-
N-(2-phenylethyl)amide;
- [4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-
10 N-[2-(N,N-dimethylamino)ethyl]amide;
 [4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-
N-[2-(p-sulphonamidophenyl)ethyl]amide;
 [4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-
N-(2-(p-sulphonylphenyl)ethyl)amide;
- 15 [4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-
N-[2-(2-pyridyl)ethyl]amide;
 [4-(N-Hydroxyamino)-2R-pentylsuccinyl]-L-β-cyclohexylalanine-N-
(2-phenylethyl)amide;
 [4-(N-Hydroxyamino)-2R-isoamylsuccinyl]-L-β-cyclohexylalanine-N-
20 (2-phenylethyl)amide;
 [4-(N-Hydroxyamino)-2R-phenylbutylsuccinyl]-L-β-cyclohexylalanine-N-
(2-phenylethyl)amide;
 [4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-
N-[3-(4-morpholinyl)propyl]amide;
- 25 [4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-
N-[β-alanine]amide;
 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-β-cyclohexylalanine amide;
 [4-(N-Hydroxyamino)-2R-(3-phenylpropyl)succinyl]-L-β-
cyclohexylalanine amide;
- 30 [4-(N-Hydroxyamino)-2R-(3-phenylbutyl)succinyl]-L-β-
cyclohexylalanine amide;

- {4-(N-Hydroxyamino)-2(R)-[3-(N-methyl-4-pyridinium)propyl]succinyl}-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;
- {4-Hydroxy-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholine-sulphonylamino)ethyl]amide;
- 5 {4-(N-Hydroxyamino)-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide;
- {4-(N-Hydroxyamino)-2-(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide;
- {4-N-Hydroxyamino)-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-dimethylsulphonylamino)propyl]amide;---
- 10 {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-[S-(methyl)penicillamine]-N-methylamide;
- {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-[S-(methyl)penicillamine]amide;
- 15 {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-penicillamine]amide;
- {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-[S-(methyl)penicillaminesulphone]-N-methylamide;
- {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-[S-(methyl)penicillaminesulphoxide]-N-methylamide;
- 20 {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-penicillamine-N-methylamide;
- {4-(N-Hydroxyamino)-2(R)-3-(2-methylpropyl)succinyl}-L-[S-methyl)penicillamine]-N-methylamide;
- 25 N⁴-Hydroxy-N¹-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-4-(chlorophenylpropyl)succinamide;
- N⁴-Hydroxy-N¹-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-(4-methylphenylpropyl)succinamide;
- N⁴-Hydroxy-N¹-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-(4-methoxyphenylpropyl)succinamide;
- 30 N⁴-Hydroxy-N¹-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-(4-trifluoromethylphenylpropyl)succinamide;

- N*-[2-Acetylmercapto-4-methoxycarbonylbutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Acetylmercapto-5-methoxycarbonylpentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- 5 *N*-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Acetylmercapto-4-phthalimidobutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-phenylalanine
- 10 *N*-methanamide;
- N*-[2-Acetylmercapto-6-phthalimidohexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2,3-bis-Mercaptopropanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Mercapto-3-methoxycarbonylpropanoyl]-*L*-leucyl-*L*-phenylalanine
- 15 *N*-methanamide;
- N*-[2-Mercapto-4-methoxycarbonylbutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Mercapto-5-methoxycarbonylpentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- 20 *N*-[2-Mercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Mercapto-4-phthalimidobutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-phenylalanine
- 25 *N*-methanamide;
- N*-[2-Mercapto-6-phthalimidohexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Acetylmercapto-5-methoxycarbonylpentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- 30 *N*-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methanamide;
- N*-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-*L*-valinyl-*L*-phenylalanine *N*-methanamide;

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N-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-5-methyl-*L*-glutamic acid *N*-methylamide;

N-[2-Mercapto-6-phthalimidohexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

5 *N*-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(3-picolyl)amino]-3-methylbutanamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-3-picolyl)amino]-2-cyclohexylacetamide;

10 *N*-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(benzyl)amino]-4-methylpentanamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(benzyl)amino]-6-[(*N,N*-dimethylglycyl)amino]hexanamide hydrochloride;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(3-picolyl)amino]-3-methylbutanamide;

15 *N*-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(4-picolyl)amino]-2-cyclohexylacetamide;

N-Hydroxy-2(R)-[(4-methoxybenzenesulfonyl)-(4-picolyl)amino]-2-(2-tetrahydrofuranyl)acetamide;

20 *N*-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(3-picolyl)amino]-3-methylbutanamide;

[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-methylsuccinyl]-*N*²-(*S*)-piperazic acid *N*-methyl amide;

[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-benzylsuccinyl]-*N*²-(*S*)-piperazic acid *N*-methyl amide;

25 [4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-methoxyphenylsuccinyl]-*N*²-(*S*)-piperazic acid *N*-methyl amide;

[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-methoxybenzylsuccinyl]-*N*²-(*S*)-piperazic acid *N*-methyl amide;

30 [4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-methyl-thiophenylsuccinyl]-*N*²-(*S*)-piperazic acid *N*-methyl amide;

[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-methyl-thiobenzylsuccinyl]-*N*²-(*S*)-piperazic acid *N*-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthiobenzylsuccinyl]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-(methylthio-2-thienyl)succinyl]-N²-(S)-piperazic acid N-methyl amide;

5 [4-(N-Hydroxyamino)-2R-hexyl-3S-benzylsuccinyl]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl acetate]-N²-(S)-piperazic acid N-methyl amide;

10 [4-(N-Hydroxyamino)-2R-hexyl-3S-methylisopropanoate]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl tert-butanoate]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthioacetate]-N²-(S)-piperazic acid N-methyl amide;

15 [4-(N-Hydroxyamino)-2R-hexyl-3S-methylthioisopropanoate]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthio-tert-butanoate]-N²-(S)-piperazic acid N-methyl amide;

20 [4-(N-Hydroxyamino)-2R-hexyl-3S-methyl-(2-pyridyl)]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl-(3-pyridyl)]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl-(4-pyridyl)]-N²-(S)-piperazic acid N-methyl amide;

25 [4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylsuccinyl]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-benzylsuccinyl]-N²-(S)-piperazic acid N-methyl amide;

30 [4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methoxyphenylsuccinyl]-N²-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl acetate]-N²-(S)-piperazic acid
N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylisopropanoate]-N²-(S)-
piperazic acid N-methyl amide;

5 [4-(N-Hydroxyamino)-2R-octyl-3S-methyl tert-butanoate]-N²-(S)-
piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthioacetate]-N²-(S)-piperazic
acid N-methyl amide;

10 [4-(N-Hydroxyamino)-2R-octyl-3S-methylthioisopropanoate]-N²-(S)-
piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthio-tert-butanoate]-N²-(S)-
piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl-(2-pyridyl)]-N²-(S)-piperazic
acid N-methyl amide;

15 [4-(N-Hydroxyamino)-2R-octyl-3S-methyl-(3-pyridyl)]-N²-(S)-piperazic
acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl-(4-pyridyl)]-N²-(S)-piperazic
acid N-methyl amide;

20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N²-(S)-4'(S/R)-
benzylpiperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N²-(S)-5'(S/R)-
benzylpiperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N²-(S)-6'(S/R)-
benzylpiperazic acid N-methyl amide;

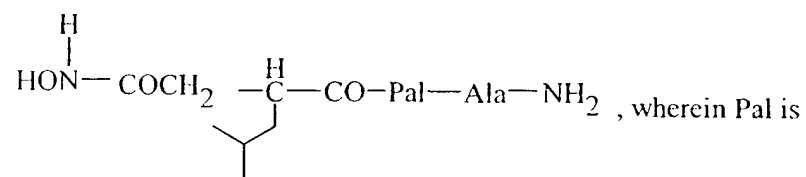
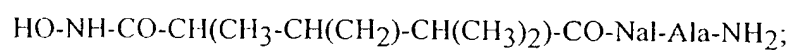
25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N²-(S)-
[5',6']benzopiperazic acid N-methyl amide;

N-[1(R)-Carboxy-ethyl]-α(S)-isobutylglycine-(S)-N²-piperazic acid
methyl amide;

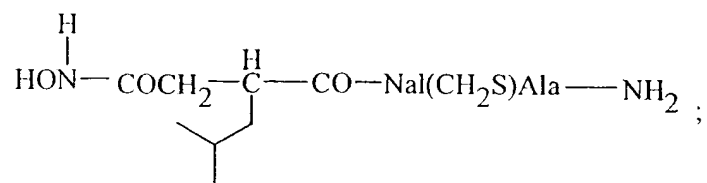
30 N-[1(R)-Carboxy-ethyl]-α(S)-hexylglycine-(S)-N²-piperazic acid methyl
amide;

- 2-[2(R)-[2-[1,1'-Biphenyl]yl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-
3(S)-methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[1,1'-Biphenyl]yl]propyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-
3(S)-methylaminocarbonyl-hexahydropyridazine;
- 5 2-[2(R)-[2-(4-Propylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-
methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-(4-Butylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-
methylaminocarbonyl-hexahydropyridazine;
- 10 2-[2(R)-[2-(4-t-Butylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-
3(S)-methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[4-(4-Fluorophenyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-
1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[4-(4-Fluorophenyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-
1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;
- 15 2-[2(R)-[2-n-Octyl-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-
methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-
3(S)-methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-
1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;
- 20 2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-
carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-
1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;
- 25 2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-
3(S)-methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-
1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;
- 2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-
carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;
- 30 2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-
1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

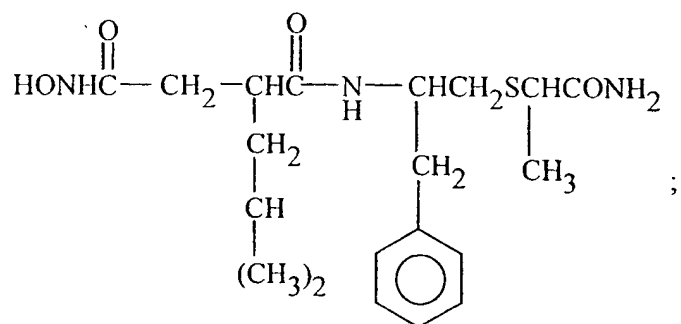
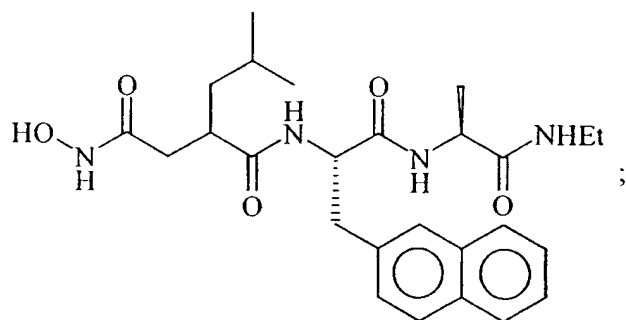
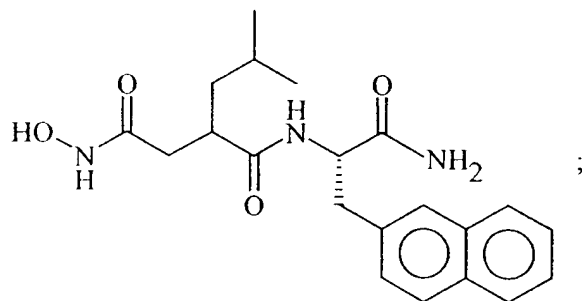
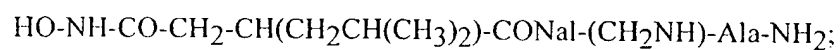
-31-



3-pyridylalanine;



5



4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(5-amino-4H-[1,2,4]-triazol-3-yl)methyl]amino]carbonyl]butyl]amino]-butanoic acid;

5 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[1-(6-oxo-1,6-dihydro-pyridazin-3-yl)ethyl]amino]carbonyl]butyl]-amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[phenyl]amino]carbonyl]butyl]amino]-butanoic acid;

10 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[benzyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[pyridin-4-ylmethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[2-(1H-imidazol-4-yl)ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

15 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[pyridin-2-ylmethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[4-sulfamoyl-phenyl]amino]carbonyl]butyl]amino]-butanoic acid;

20 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[3-sulfamoyl-phenyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[4-dimethylamino-benzyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[1-(S)-phenyl-ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

25 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[1,1-dioxo-tetrahydro-thiophen-3-yl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[4-sulfamoyl-benzyl]amino]carbonyl]butyl]amino]-butanoic acid;

30 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[1-(R)-phenyl-ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[3-fluorobenzyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(2-dimethylaminoethyl)-methyl-amino]carbonyl]butyl]amino]-butanoic acid;

5 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(1-azabicyclo[2.2.2]-oct-3(R)-amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(1-azabicyclo[2.2.2]oct-3-(S)-yl)amino]carbonyl]butyl]amino]-butanoic acid;

10 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(3-(R)-4-(S)-5-(R)-6-tetrahydro-tetrahydra-pyran-2-(R)-yl)methyl]amino]-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(N,N'-dimethyl-hydrazino)carbonyl]butyl]amino]-butanoic acid;

15 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(methoxymethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(dimethylamino)carbonyl]butyl]amino]-butanoic acid;

20 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(2-oxo-tetrahydro-thiophen-3-(R)-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(2-oxo-tetrahydro-thiophen-3-(S)-yl)amino]carbonyl]butyl]amino]-butanoic acid;

25 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(3-(R)-acetyl-amino-4-(S)-5-(S)-dihydroxy-6-(R)-hydroxymethyl-tetrahydro-pyran-2-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[benzyl(2-hydroxyethyl)amino]carbonyl]butyl]amino]-butanoic acid;

30 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[3,4-dihydro-1H-isoquinoline-2-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[4-methylpiperazine-1-carbonyl]butyl]amino]-butanoic acid;

- 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[(pyridine-3-carbonyl-hydrazino)carbonyl]butyl]amino]-butanoic acid;
- 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[(benzenesulfonyl)amino]carbonyl]butyl]amino]-butanoic acid;
- 5 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[4-(aminobenzyl)amino]carbonyl]butyl]amino]-butanoic acid;
- 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[4-(trifluoro-methanesulfonylamino)benzyl]amino]carbonyl]butyl]amino]-butanoic acid;
- 10 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[2-hydroxy-(R)-bicyclo[4.3.0]nona-3,6(1)-diene]amino]carbonyl]butyl]-amino]-butanoic acid;
- 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[2-hydroxy-(S)-bicyclo[4.3.0]nona-3,6(1)-diene]amino]carbonyl]butyl]-amino]-butanoic acid;
- 15 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[N-methyl-pyrrolidine)-methyl-amino]carbonyl]butyl]amino]-butanoic acid;
- 4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[(N-ethoxycarbonylmethyl-piperazine)-1-carbonyl]butyl]amino]-butanoic acid;
- 20 2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-bromo-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;
- 2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-propoxy-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;
- 25 2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;
- 2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-amino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;
- 30 2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;
- 2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

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H₂NCON(OH)CH₂CH₂CH(iBu)-CO-L-TrpNHMe;

CH₃CON(OH)CH(iBu)-CO-L-TrpNHMe;

CH₃CON(OH)CH₂CH(iBu)-CO-L-TrpNHMe;

CH₃CON(OH)CH₂CH₂CH(iBu)-CO-L-TrpNHMe;

5 NHOHCOCH₂CH(i-Bu)CO-L-Trp-NHMe;

HONHCONHCH₂CH(i-Bu)CONHCHCOOH or



ROOCCH₂CH(i-Bu)CONHCHCOOH;

10



N-{D,L-2-(Hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-(2'-naphthyl)alanyl-L-alanine, 2-(amino)ethyl amide;

15 N-{D,L-2-(Hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine, 2-(amino)ethyl amide;

4(S)-[3-Hydroxyaminocarbonyl-2(R)-(2-methylpropyl)propanoyl]amino-1,2,3,4,5-tetrahydro-3H-2-benzazepin-3-one;

[4-(N-Hydroxyamino)-(2R)-isobutyl-3-methylsuccinyl]-L-phenylglycine-N-methylamide;

20 4(S)-[2(R)-[1(R)-Hydroxycarbamoyl-2-morpholinoethyl]-4-methylvaleryl]amino-1,2,4,5-tetrahydro-3H-2-benzazepine-3-one;

(1R,4S)-4-[(2R)-Hydroxycarbamoylmethyl-4-methylvaleryl]amino-3-oxo-1,2,4,5-tetrahydro-3H-2-benzazepine-1-carboxylic acid;

3-[2-(N-Methylcarbamoyl)ethylsulfinyl]-5-methylhexanohydroxamic acid;

25 N-[(2-Thenoylmercapto-3-methyl)-butanoyl]-homocysteine thiolactone;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-isoleucine, N-phenylamide;

30 N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-alanine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-(3-hydroxyphenyl)-ethyl)glycine-(S)-leucine, N-phenylamide hydrochloride;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-(4-methylphenyl)-ethyl)glycine-(S)-leucine, N-phenylamide hydrochloride;

5 N-[1(R)-Carboxy-ethyl]- α -(S)-(2-(2'-thienyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-(4-ethylphenyl)ethyl)glycine-(L)-leucine, N-phenylamide;

10 N-[1(R)-Carboxy-5-(1-oxo-isindolin-2-yl)pentyl]- α -(S)-(2-(4-propylphenyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-(4-chlorophenyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine- α -(S)-(2-cyclohexyl-ethyl)glycine, N-phenylamide;

15 N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine- α -(S)-(cyclohexyl)glycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine- α -(S)-(cyclohexylmethyl)glycine, N-phenylamide;

20 N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine-(L)- β -naphthylalanine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine-(L)- α -naphthylalanine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine-[(L)-glutamic acid, α,δ -bis-N-phenylamide;

25 N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-cyclohexylamide;

N-[(1(R)-Carboxy-ethyl)]- α -(S)-(2-phenyl-ethyl)glycine- α -(S)-(4-hydroxyphenyl-ethyl)glycine, N-phenylamide;

30 N-[1(R)-Carboxy-ethyl]- α -(S)-(2-phenyl-ethyl)glycine-(L)-phenylglycine, N-phenylamide;

- (2-((Hydroxy(methyl)phosphinyl)methyl)-4-phenylbutanoyl)-L-leucine,
N-phenylamide;
- [[Hydroxy[1(R)-[N-(N-acetyl-L-prolyl-L-alanyl)-amino]-ethyl]-
phosphinyl]-methyl]-4-phenyl-butanoyl-L-leucyl, N-phenylamide;
- 5 [Hydroxy-[N-(N-(benzoyl)-L-prolyl)aminobutyl]phosphinyl]methyl]-
4-phenyl-butanoyl-L-leucine, N-phenylamide;
- [Hydroxy-[2-Methylpropyloxycarbonyl-aminobutyl]-phosphinyl]methyl]-
4-phenylbutanoyl-L-leucine, N-phenylamide;
- [Hydroxy-[1-Methylethylaminocarbonyl-aminobutyl]-phosphinyl]methyl]-
10 4-phenylbutanoyl-L-leucine, N-phenylamide;
- N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucinamide;
- N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucine, N-phenylamide;
- N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucine, N-benzylamide;
- N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucine, N-(2-phenylethyl)amide;
- 15 N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalaninamide;
- N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalanine N-phenylamide;
- N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalanine N-benzylamide;
- N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalanine-b-alanine;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(L-leucine,
20 N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(2(S)-t-
butyl)glycine, N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(2(S)-t-
butyl)glycine, N-(4-pyridylamide)amide;
- 25 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(L-arginine,
N-methylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid
1-(L-leucine, N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid
30 1-(2(S)-t-butyl)glycine, N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid
1-(2(S)-(4-thiazolylmethyl)glycine, N-phenylamide)amide;

- 2(R)-(2-(4-(1-n-Propyl)phenyl)propyl)-1,5-pentanedioic acid 1-(2(S)-tert-butyl-glycine, N-4-pyridyl)amide)amide;
- 2(R)-(3-(4-(1-n-Propyl)phenyl)propyl)-1,3-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;
- 5 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-hexyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-butyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;
- 10 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(3-methylbenzyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(2-benzimidazolyl)butyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(2-benzthiazolyl)butyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;
- 15 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(2-benzoxazolyl)butyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-phenylamide)amide 9-piperidineamide;
- 2(R)-(2-(4-(1-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-phenylamide;
- 20 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-tert-butylamide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-benzylamide;
- 25 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-morpholineamide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(1(R)-phenylethyl)amide;
- 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(1(S)-phenylethyl)amide;
- 30 2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(N-methyl-N-phenyl)amide;

- N-[1(R)-Carboxyethyl]- α -(S)-(9-amino-n-nonyl)]glycine-(L)-leucine,
N-phenylamide;
- N-[1(R)-Carboxyethyl]- α -(S)-(n-octyl)]glycine-(L)-leucine,
N-phenylamide;
- 5 N-[1(R)-Carboxyethyl]- α -(S)-(n-octyl)]glycine-(L)-arginine,
N-phenylamide;
- N-[1(R)-Carboxyethyl]- α -(S)-(9-amino-n-nonyl)]glycine-(L)-arginine,
N-phenylamide;
- 10 N-[1(R)-Carboxyethyl]- α -(S)-(n-decyl)]glycine-(L)-leucine,
N-phenylamide;
- 1-(2-(4-Propylphenyl)ethyl)cyclopentane-1,3-dicarboxylic acid 1-(L-
leucine, N-phenylamide)amide;
- 1-(2-(4-Propylphenyl)ethyl)cyclohexane-1,3-dicarboxylic acid 1-(L-
leucine, N-phenylamide)amide;
- 15 N-[1(R)-Carboxyethyl]- α -(S)-2-(4-fluorobiphenyl)-glycyl-(S)-2-(*tert*-
butyl)glycine, N-phenylamide;
- 3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxy-
3,4-dihydrocarbostyryl;
- 3S-[4-(N-Hydroxyamino)-2R-isobutyl-3S-acetylthiomethylsuccinyl]-
20 amino-3,4-dihydrocarbostyryl;
- 3S-[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]amino-
1-methoxy-3,4-dihydrocarbostyryl;
- 3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxymethyl-
3,4-dihydrocarbostyryl;
- 25 1-Carboxymethyl-3S-[4-N-hydroxyamino)-2R-isobutyl-3S-
methylsuccinyl]amino-3,4-dihydrocarbostyryl;
- 3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-
1-methoxyethoxymethyl-3,4-dihydrocarbostyryl;
- 3S-[4-(N-Hydroxyamino)-2R-heptylsuccinyl]amino-1-methoxy-
30 3,4-dihydrocarbostyryl;
- 7-Chloro-3S-[4-(N-hydroxyamino)-2R-isobutylsuccinyl]amino-
1-methoxymethyl-3,4-dihydrocarbostyryl;

2-(R)-2-[(2-Carboxyethyl)(4-methoxybenzene-sulfonyl)amino]-
N-hydroxy-3-methylbutyramide;

[(2-Carboxyethyl)(3,4-dimethoxybenzene-sulfonyl)amino]-N-hydroxy-
acetamide;

5 2-(R)-2-[(2-Carbamoyl)ethyl)(4-methoxybenzene-sulfonyl)amino]-N-
hydroxy-3-methylbutyramide;

2-(R), 3-(R)-3, N-Dihydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-
piperidin-1-ylpropyl)amino]-butyramide;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)[3-(methylpyridin-
10 3-ylmethylcarbamoyl)propyl]amino]-3-methylbutyramide;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)[2-
(methylcarboxymethylcarbamoyl)ethyl]amino]-3-methyl-butylamide;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)[(1-
methylpiperidin-4-ylcarbamoyl)methyl]amino]-3-methylbutylamide;

15 2-(R)-N-Cyclohexyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-
[3-(4-methylpiperazin-1-yl)-3-oxopropyl]amino]-acetamide;

2-(R)-N-Hydroxy-2-[(methoxybenzenesulfonyl)(3-morpholin-4-yl-
[3-oxopropyl)amino]-4-(morpholin-4-yl)butylamide;

[4-(N-Benzyloxyamino)-2(R)-isobutylsuccinyl]-L-leucyl-L-alanine ethyl
20 ester;

[4-(N-Benzyloxyamino)-2(R)-isobutylsuccinyl]-3(RS)-aminolauro lactam;

Na^a-[4-(N-Benzyloxyamino)-2(R)-isobutylsuccinyl]-N^e-(N-
benzyloxycarbonylglycyl)-L-lysyl-L-alanine ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine ethyl
25 ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine
isopentylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-valylglycine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine
30 ethylamide;

Na^a-[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-N^e-
tert.butoxycarbonyl-L-lysylglycine ethylamide;

[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-3(RS)-aminooctahydro-2H-azonin-2-one;

[4-(N-Hydroxyamino)-3(S)-methyl-2(R)-isobutyl-succinyl]-L-leucylglycine ethyl ester;

5 [(3-Aminophthalimido)methyl][(RS)-4-methyl-2-[(S)-3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid;

[(RS)-4-Methyl-2-[(S)-3-methyl-1-(methyl-carbamoyl)butyl]-carbamoyl]pentyl](1,8-naphthalenedi-carboximidomethyl)phosphinic acid;

10 [(R or S)-4-Methyl-2-[(R or S)-2-oxo-3-azacyclotridecyl]-carbamoyl]pentyl](1,8-naphthalenedicarboximidomethyl)phosphinic acid;

N-[N-[(R or S)-2[[[N-[1-(Benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]hydroxyphosphinyl]-methyl]-4-methylvaleryl]-L-leucyl]-L-alanine;

15 [[1,4-Dihydro-2,4-dioxo-3(2H)-quinazolinyl]-methyl][[(R or S)-4-methyl-2-[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid;

N²-[(R)-Hydroxycarbamoylmethyl]-4-methylvaleryl]-N¹,3-dimethyl-L-valinamide;

20 N²-[2(R or S)-[[[(5-Bromo-2,3-dihydro-6-hydroxy)-1,3-dioxo-1H-benz[d,e]isoquinol-2-yl)methyl]-(hydroxy)phosphinyl]methyl]-4-methylvaleryl]-N¹,3-dimethyl-L-valinamide;

N²-[(R or S)-[(R)-(Amino)(5-bromo-2,3-dihydro-6-hydroxy-1,3-dioxo-1H-benz[d,e]isoquinol-2-yl)methyl](hydroxy)phosphinyl]methyl]-4-methylvaleryl]-N³,1-dimethyl-L-valinamide hydrobromide;

25 N²-[2(R or S)-[1(S)-(Hydroxycarbamoyl)ethyl-4-methylvaleryl]-N¹,3-dimethylvalinamide;

N²-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N¹,3-dimethyl-L-valinamide;

N²-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-4-(methoxycarbonyl)butyl]-4-methylvaleryl]-N¹,3-dimethyl-L-valinamide;

30 M²-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-4-phenyl-butyl]-4-methylvaleryl]-N¹,3-dimethyl-L-valinamide;

- [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-leucine methylamide;
[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-leucine neopentylamide;
[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-alanyl-L-leucine
ethylamide;
- 5 [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-(N^e-phthaloyl)-
lysyl-L-leucine ethylamide;
 [4-(N-Hydroxyamino)-2(RS)-undecylsuccinyl]-L-leucyl-L-leucine
ethylamide;
- 10 [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-phenylalanyl-L-leucine
ethylamide;
 [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-nonanyl-L-leucine
ethylamide;
- [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-phenylalanine
tert.butylamide;
- 15 [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-tert.butylglycine
methylamide;
 [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-neopentylglycine
methylamide;
- [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-homophenylalanyl-L-
20 leucine ethylamide;
 [4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-cyclohexylalanine
methylamide;
- [4-(N-Hydroxyamino)-2(RS)-isooctylsuccinyl]-L-phenylalanine
methylamide;
- 25 [4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-L-neopentylglycine
methylamide;
- [4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-(D or L)-
β,β-dimethylphenylalanine methylamide;
- [4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-(D or L)-threo-
30 β-methylphenylalanine methylamide;
- [4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-DL-erthro-
β-methylphenylalanine methylamide;

- 3-[3-Cyclopropyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-3-azabicyclo[3.2.2]nonane;
- 3-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-3-azabicyclo[3.2.2]nonane;
- 5 1-[3-Cyclohexyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]piperidine;
- 4-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]tetrahydro-1,4-thiazine;
- 4-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]tetrahydro-1,4-thiazine
- 10 S,S-dioxide;
- 4-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]tetrahydro-1,4-thiazine;
- 3-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-5,5-dimethyl-N-propyl-
- 15 [4(R)-thiazolidinecarboxamide;
- 4-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]morpholine;
- 3-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-N,5,5-trimethyl-4(R)-
- 20 thiazolidinecarboxamide;
- 4-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-4-phenylpiperazine;
- 4-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]morpholine;
- 25 1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]pyrrolidine;
- 8-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-1,4-dioxo-8-
- 30 azaspiro[4,5]decane;
- 1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-4-methoxypiperidine;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

5 Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

1-[2(R or S)-[1(S)-(Hydroxycarbamoyl)ethyl]undecanoyl]piperidine;

1-[2-(R or S)-[1(S)-(Hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]-piperidine;

10 Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide;

15 1-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-piperidine;

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-morpholine;

1-(Benzyloxycarbonyl)-hexahydro-2-[2(R)-[(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(α (S)-methylbenzyl)-3(S)-pyridazinecarboxamide;

20 N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-5-(carboxy)pentanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;

25 N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(propylamino)-6-(oxo)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-(6RS)-6-(hydroxy)heptanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(hydroxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

30 (2S)-N-2-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-
 [(4-methyl)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid
 N-2-(4'-sulfamoyl)phenylethylamide;

5 (2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-
 [(1-oxo)butylamino]hexanoyl]amino-3-cyclohexylpropionic acid
 N-2-(4'-sulfamoyl)phenylethylamide;

(2S)-N-2-[(2'R)-2'-[(1''S)-1''-(Methyl)-2''-(hydroxyamino)-2''-
 (oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid
 N-methylamide;

10 (2S)-N-2-[(2'R)-2'-[(1''S)-1''-(2-Methylpropyl)-2''-(hydroxyamino)-
 2''-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid
 N-methylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenoxy)hexanoyl]-L-
 phenylalanine N-methylamide;

15 N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-7-(phenoxy)heptanoyl]-L-
 phenylalanine N-methylamide;

(2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-
 (phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-
 phenylethylamide;

20 (2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-
 (phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-
 sulfamoyl)phenylethylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-5-(phenylmethoxy)-
 pentanoyl]-L-phenylalanine N-methylamide;

25 N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-7-(phenylmethoxy)-
 heptanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(phenyloxy)hexanoyl]-
 L-phenylalanine N-methylamide;

30 N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-7-[(phenyloxy)heptanoyl]-
 L-phenylalanine N-methylamide;

(2S)-N-2[(2'R)-[(1''R)-1''-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl-2''-(hydroxyamino)-2''-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]-amino-3,3-dimethylbutanoic acid N-methylamide;

5 N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(oxo)-6-(propylamino)hexanoyl]-L-phenylalanine N-2-phenylethylamide;

(2S)-N-2-[(2'R)-2'-[(1''S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

10 (2S)-N-2-[(2'R)-2'-[(1''S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6'-(oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

(2S)-N-2-[(2'R)-2'-[(1''S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6'-(oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;

15 (2S)-N-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4'-sulfamoyl)phenylethylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6'-(phenylmethoxy)-hexanoyl]-L-(3,5-dimethyl)phenylalanine N-2-(4'-sulfamoyl)phenylethylamide;

20 (2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-[(4-methoxy)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;

(2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-[(4-methyl)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;

25 (2S)-N-2'-[(2'R)-2'-[2''-(Hydroxyamino)-2''-(oxo)ethyl]-6'-[(1-oxo)butylamino]hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4'-sulfamoyl)phenylethylamide;

30 (2S)-N-2-[(2'R)-2'-[(1''S)-1''-(Methyl)-2''-(hydroxyamino)-2''-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2*S*)-*N*-2'-[(2'*R*)-2'-(Carboxymethyl)-6'-(3-methylphenoxy)hexanoyl]-amino-3,3-dimethylbutanoic acid *N*-methylester;

(3*R*,10*S*)-5-Methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanoic acid;

5 (3*R*,10*S*)-*N*-Hydroxy-5-methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanamide;

(3*R*,11*S*)-*N*-Hydroxy-5-methyl-3-(10-oxo-1,9-diazatricyclo[11.6.1.0]eicosa-13(20),14(19),15,17-tetraen-11-ylcarbamoyl)hexanamide;

10 (3*R*,9*S*)-5-Methyl-3-(8-oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12(17),13,15-tetraen-9-ylcarbamoyl)hexanoic acid;

(3*R*,9*S*)-*N*-Hydroxy-5-methyl-3-(8-oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12(17),13,15-tetraen-9-ylcarbamoyl)hexanamide;

15 (10*S*)-[4-Methyl-2-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)pentyl]-(quinolin-2-ylthiomethyl)phosphinic acid;

(3*R*,10*S*)-*N*-Hydroxy-5-methyl-2-methoxycarbonyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)-hexanamide;

20 *N*-(4-Methyl-2-carboxymethylpentanoyl)-*L*-leucine-*N'*-(4-methoxycarbonylphenyl)carboxamide;

N-(4-Methyl-2-(*N''*-hydroxycarbamoyl)methylpentanoyl)-*L*-leucine-*N'*-(4-methoxycarbonylphenyl)carboxamide;

N-(4-Methyl-2-(*N''*-hydroxycarbamoyl)methylpentanoyl)-*L*-leucine-*N'*-(4-carboxyphenyl)carboxamide;

25 *N*-(4-Methyl-2-(*N''*-hydroxycarbamoyl)methylpentanoyl)-*L*-tryptophan-*N'*-(4-carboxyphenyl)carboxamide;

N-(4-Methyl-2-(*N''*-hydroxycarbamoyl)methylpentanoyl)-*L*-cyclohexylglycine-*N'*-(4-methoxycarbonylphenyl)carboxamide;

30 *N*-(4-Methyl-2-(*N''*-hydroxycarbamoyl)methylpentanoyl)-*L*-*t*-leucine-*N'*-(4-methoxycarbonylphenyl)carboxamide;

(3*R*,10*S*)-6-Biphenyl-4-yl)-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanoic acid;

(3R,10S)-*N*-Hydroxy-5-methyl-2-methoxycarbonyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)-hexanamide;

5 (3R,9S)-5-Methyl-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-Cyclobutylmethyl-*N*-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)succinamic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-5-phenoxy-pentanoic acid;

10 (3R,9S)-5-(4-Chlorophenoxy)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid;

(3R,9S)-5-(4-Chlorophenoxy)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid ethyl ester;

15 (3R,9S)-3-(8-Oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid ethyl ester;

(3R,9S)-6-(4-Hydroxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-pyridin-4-yl-hexanoic acid;

20 (3R,9S)-6-[4-(3-Hydroxy-propoxy)-phenyl]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-5-(4-phenoxy-phenyl)pentanoic acid;

25 (3R,9S)-6-[4-(2-Hydroxy-ethoxy)-phenyl]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-[4-(2-pyrrolidin-1-yl-

30 ethoxyphenyl]hexanoic acid;

(3R,9S)-6-(4-Methoxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

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(3R,9S)-5-(4-Methoxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid;

(3R,9S)-6-(4-Amino-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

5 (3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-[4-(pyridin-4-ylmethoxy)phenyl]-hexanoic acid;

(3R,9S)-6-(4-Acetylamino-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic
10 acid;

N^{α} -[[3-(N-Hydroxycarbamoyl)-4-methylthio-2-propoxymethyl]butyl]-N,O-dimethyltyrosine amide;

N^{α} -[[3-(N-Hydroxycarbamoyl)-4-isopropylthio-2-propoxymethyl]-butyl]-N,O-dimethyltyrosine amide;

15 N^{α} -[[3-(N-Hydroxycarbamoyl)-2-propylthio]butyl]-N,O-dimethyltyrosine amide;

N-[N-(1-Phosphono-3-phenylpropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

20 N-[N-(1-Phosphono-3-(4-bromo-1,8-naphthalene-dicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide;

N-[N-(1-Phosphono-3-(benzyloxycarbonylamino)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide;

N-[N-(1-Phosphono-3-(2-hydroxyphenyl)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide;

25 N-[N-(1-Phosphono-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

N-[N-(1-Phosphono-3-(methylsulphinyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

30 N-[N-(1-Phosphono-3-(methylsulphonyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-tryptophan-N-methylamide;

-69-

- US 5,256,657 (Sterling Winthrop)
US 5,300,674; US 5,412,145 (British Biotechnology)
US 5,387,610; US 5,616,605 (Research Corporation Technologies)
US 5,442,110; US 5,473,100 (Yamanouchi)
5 US 5,643,908 (Sankyo)
US 5,525,629 (British Biotechnology)
US 5,569,665 (Celltech)
US 5,530,128 (Celltech)
US 5,318,964; US 5,447,929 (Roche)
10 US 5,643,964; US 5,700,838 (British Biotechnology)
WO 97/27174 (Shionogi)

An especially preferred group of compounds to be employed in the present method are those described in WO 95/35275 and WO 95/35276, both of which are incorporated herein by reference. Typical compounds from within these groups to
15 be employed include:

- N-Hydroxy-2-[[[(2-(4-methoxy-phenoxy)-ethyl)-(toluene-4-sulfonyl)-amino]-acetamide;
N-Hydroxy-2-[(4-phenoxy-ethyl)-toluene-4-sulfonyl amino]-acetamide;
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-nonyl-amino]-acetamide;
20 2-[Decyl-(toluene-4-sulfonyl)-amino]-N-hydroxy-acetamide;
2-Benzyl-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;
N-Hydroxy-2-[(2-methoxy-benzyl)-(octane-1-sulfonyl)-amino]-acetamide;
2-[(2-Ethoxy-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;
N-Hydroxy-2-[(naphthalen-2-yl-methyl)-(octane-1-sulfonyl)-amino]-
25 acetamide;
2-[(4-Chloro-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide,
and salts, solvates, or hydrates thereof.

Another class of matrix metalloproteinase inhibitors are aryl sulfonamides of the formula

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4-N-Hydroxy-carbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-piperidine trifluoroacetate;

4-N-Hydroxy-carbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[t-butoxycarbonyl]-piperidine;

5 4-N-Hydroxycarbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[methylsulfonyl]-piperidine;

N-Hydroxycarbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[4-picolyl]-piperidine hydrochloride;

10 N-Hydroxycarbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)amino]-1-[morpholinocarbonyl]-piperidine hydrochloride; and

N-(t-Butyloxy)-2-[[4-methoxybenzenesulfonyl (benzyl)amino]-2-[2-(4-morpholino)ethyl]acetamide.

The following compounds are prepared similarly to Example 7:

15 N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)-amino]-2-(2-(4-morpholino)ethyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)-amino]-2-(2-(4-morpholino)ethyl]acetamide dihydro-chloride;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride;

20 N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methyl-thiazol-4-ylmethyl)amino]-2-[2-(4-morpholino) ethyl]acetamide dihydrochloride;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl]benzyl)amino]-2-[2-(4-thiomorpholino)ethyl]acetamide;

25 N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-methylthiazol-4-ylmethyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl(benzyl)amino]-2-[(6-chloropiperonyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl(benzyl)amino]-2-[(1-pyrazolyl)methyl]acetamide;

30 N-Hydroxy-2-[[4-methoxybenzenesulfonyl(3-picolyl)amino]-2-[3-picolyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl(benzyl)-amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride;

N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-L-tryptophan
amylamide;

N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-L-tryptophan
piperidinamide;

5 N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-L-tryptophan
dodecylamide;

N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-L-
tryptophan(S)-methylbenzylamide;

10 N-[L-2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-L-
tryptophan(6-phenylmethoxycarbonyl-amino-hexyl-1)amide;

2S-Hydroxy-3R-[1S-(3-methoxy-2,2-dimethyl-propylcarbamoyl)-
2,2-dimethyl-propylcarbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-
6-(4-chloro)phenyl-hexanohydroxamic acid;

15 2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-
octanohydroxamic acid;

2S-Hydroxy-3R-[1S-(pyridin-2-ylmethylcarbamoyl)-2,2-dimethyl-
propylcarbamoyl]-5-methyl-hexanohydroxamic acid;

20 2S-Hydroxy-3R-[1S-(pyridin-3-ylmethylcarbamoyl)-2,2-dimethyl-
propylcarbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(pyridin-4-ylmethylcarbamoyl)-2,2-dimethyl-
propylcarbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-
4-methoxy-butanohydroxamic acid;

25 2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-
4-benzyloxy-butanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-
4-benzylthio-butanohydroxamic acid;

30 2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-buten-
3-ylcarbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(*tert*-butylcarbamoyl)-2,2-dimethyl-
propylcarbamoyl]-5-methyl-hexanohydroxamic acid;

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[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(2-hydroxyethyl)amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalaninyl-D-prolinol;

5 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide sodium salt;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide;

10 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide or a salt thereof;

N^2 -[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]- N^6 -*tert*-butyloxycarbonyl-L-lysine- N^1 -methylamide;

15 N^2 -[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]- N^6 -*tert*-butyloxycarbonyl- N^6 -(4-hydroxyphenylthiomethyl)-L-lysine- N^1 -methylamide;

N^2 -[4-(N-Hydroxyamino)-3S-(2-thienylthiomethyl)-2R-isobutylsuccinyl]- N^6 -*tert*-butyloxycarbonyl-L-lysine- N^1 -methylamide;

N^2 -[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]-O-*tert*-butyl-L-threonine- N^1 -methylamide;

20 N^2 -[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]-L-glutamine- N^1 , N^5 -dimethylamide;

N^2 -[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylsulphonylmethyl)-2R-isobutylsuccinyl]- N^6 -acetyl-L-lysine- N^1 -methylamide;

25 3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

3R-(1S-Methylcarbamoyl-2-thien-2-yl-ethylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

3R-(3-Methyl-1S-methylcarbamoyl-butylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

30 2S-[1S-Methylcarbamoyl-2-oxadiazol-5-yl-ethylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-oxymethylcarboxyglycine)phenylalanine-N-methylamide;
- 5 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-4-oxymethylnitrile)-phenylalanine-N-methylamide;
- 10 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-(2-methyloxycarbonyl)-ethyl)-4-methoxyphenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-3-(hydroxymethyl)-4-methoxyphenylalanine-N-methylamide;
- 15 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-3-methyl-4-methoxyphenylalanine-N-methylamide;
- 2-[Benzyl-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;
- N-Hydroxy-2-[(2-methoxy-benzyl)-(octane-1-sulfonyl)-amino]-acetamide;
- 2-[(2-Ethoxy-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;
- 20 N-Hydroxy-2-[(naphthalen-2-yl-methyl)-(octane-1-sulfonyl)-amino]-acetamide;
- 2-[(4-Chloro-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;
- N²-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-leucine-N¹-methylamide;
- 25 N²-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-5-methyl-L-glutamic acid-N¹-methylamide;
- N²-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N¹-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thienylthiomethyl)succinyl]-L-phenylalanine-N-methylamide;
- 30 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide;

- 3R-(2-Phenyl-1S-[2-oxo-pyrolid-1-yl]-propylcarbamoyl-ethylcarbamoyl)-
5-methyl-hexanohydroxamic acid;
- 3R-(2-[4-Methoxy-phenyl]-1S-methylcarbamoyl-ethylcarbamoyl)-
5-methyl-hexanohydroxamic acid;
- 5 3R-(2-Phenyl-1S-[pyrid-3-ylmethylcarbamoyl]-ethylcarbamoyl)-5-methyl-
hexanohydroxamic acid;
- 3R-(2,2-Dimethyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-
hexanohydroxamic acid;
- Isobutylmalonoyl-L-alanine-furfurylamide hydroxamate;
- 10 2-Isobutyl-3-carbonyl-3'-(4-acetylaniline)propionic acid; ...
- N-Benzyloxycarbonyl- α -phosphonoglycyl-L-alanine furfurylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)succinyl]-L-
phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenylthiomethyl)-
15 succinyl]-L-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-
succinyl]-L-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-dimethylphenylthiomethyl)-
succinyl]-L-phenylalanine-N-methylamide;
- 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenylthiomethyl)-
succinyl]-L-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthiomethyl)-
succinyl]-L-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methylphenylthiomethyl)-
25 succinyl]-L-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-amino-
phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide;
- [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphinylmethylsuccinyl]-L-
phenylalanine-N-methylamide;
- 30 3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-
5-methyl-2S-phenylsulfanylmethyl- hexanohydroxamic acid;
- 3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-
5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanohydroxamic acid;

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[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenylalanine-N-(1-(3-aminopropyl)-imidazole)amide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenylalanine-N-(2-aminomethylbenzimidazole)amide;

5 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholino]amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide;

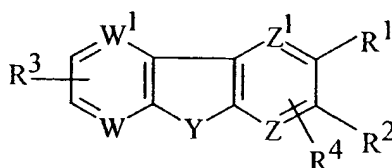
10 [4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide;

[4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenylalanine-N-[4-(2-aminopropyl)-morpholine]amide;

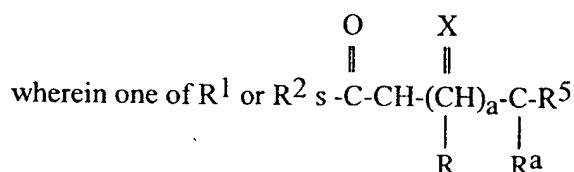
[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(3-aminomethylpyridine)amide hydrochloride; and

15 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide hydrochloride.

In a preferred embodiment, tricyclic butyric acid derivatives which are inhibitors of matrix metalloproteases are employed in the instant invention. A preferred group of tricyclic butyric acid derivatives are defined by the formula:



20



25

wherein X is O,

N-OR⁶ wherein R⁶ is hydrogen,

-(CH₂)_n-aryl wherein n is zero or an integer of 1 to 5,

alkyl, or

30

-(CH₂)_n-cycloalkyl wherein n is as defined above, or

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$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-C-R} \end{array}$$
 wherein R is as defined above,

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-C-N-R}^6 \\ \parallel \\ \text{R}^{6a} \end{array}$$
 wherein R^6 and R^{6a} are each the same or

different and are as defined above for R^6 , or

$$\begin{array}{c} \text{-(CH}_2\text{)}_n\text{-N-R}^6 \\ | \\ \text{R}^{6a} \end{array}$$
 wherein R^6 and R^{6a} are each the same or

different and are as defined above for R^6 ;

W , W^1 , Z , and Z^1 are each the same or different and each is CR^3 wherein R^3 is as

defined above, or

N providing only one of W or W^1 is

N and/or only one of Z or Z^1 is N; and

Y is -N- wherein R is as defined above,

$\begin{array}{c} | \\ \text{R} \end{array}$

-O- ,

$\text{-S(O)}_m\text{-}$ wherein m is zero or an integer of 1 or 2,

$\text{-CH}_2\text{-}$,

-C- ,

$\begin{array}{c} | \\ \text{O} \end{array}$

-C- wherein R^6 is as defined above,

$\begin{array}{c} | \\ \text{N-OR}^6 \end{array}$

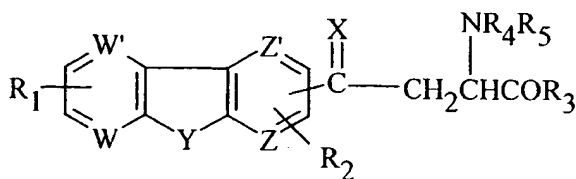
-CH- wherein R^6 is as defined above,

$\begin{array}{c} | \\ \text{OR}^6 \end{array}$

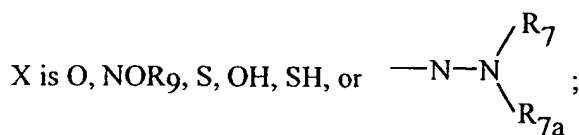
-85-

- 2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-4-methyl-pentanoic acid;
 2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-phenyl-pentanoic acid;
 4-Dibenzofuran-2-yl-4-hydroxyimino-2-phenethyl-butyric acid;
 5-(4-Chloro-phenyl)-2-(2-dibenzofuran-2-yl-2-hydroxyimino-ethyl)-
 5 pentanoic acid;
 2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-(4-fluoro-phenyl)-
 pentanoic acid;
 2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-(4-methoxy-phenyl)-
 pentanoic acid;
 10 2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-p-tolyl-pentanoic acid;
 3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-5-methyl-hexanoic acid;
 3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-phenyl-hexanoic acid;
 3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-5-phenyl-pentanoic acid;
 6-(4-Chloro-phenyl)-3-(dibenzofuran-2-yl-hydroxyimino-methyl)-
 15 hexanoic acid;
 3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-(4-fluoro-phenyl)-
 hexanoic acid;
 3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-(4-methoxyphenyl)-
 hexanoic acid; and
 20 3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-p-tolyl-hexanoic acid; and
 corresponding isomers thereof;
 or a pharmaceutically acceptable salt thereof.

Tricyclic butyric acids having an α -amino substituent are defined by the formula:



wherein:



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C₁-C₂₀ alkyl or substituted C₁-C₂₀ alkyl,(CH₂)₀₋₆-aryl,(CH₂)₀₋₆-heteroaryl; or one of R₄ and R₅ is hydrogen and the other is:COR₈,5 CSR₈,CONR₈R₉,CSNR₈R₉,COOR₈,COSR₈,10 COCHR₈,
$$\begin{array}{c} | \\ \text{NR}_1\text{R}_2 \end{array}$$
CON-CONR₈R₉,
$$\begin{array}{c} | \\ \text{R}_1 \end{array}$$
15
CON-COOR₈,
$$\begin{array}{c} | \\ \text{R}_1 \end{array}$$
CON-COSR₈, or
$$\begin{array}{c} | \\ \text{R}_1 \end{array}$$
20
CON-SO₂NR₈R₉;
$$\begin{array}{c} | \\ \text{R}_1 \end{array}$$
25 CON-SO₃R₈;
$$\begin{array}{c} | \\ \text{R}_1 \end{array}$$

Y is -N-,

$$\begin{array}{c} | \\ \text{R}_1 \end{array}$$
30

-O-,

-S(O)_{0, 1 or 2},-CH₂-

(CH₂)₀₋₆-aryl,
(CH₂)₀₋₆-heteroaryl, or
(CH₂)₀₋₆-cycloalkyl;

W, W¹, Z, and Z¹ independently are CR₁ or N;

5 and the pharmaceutically acceptable salts, isomers, stereoisomers, and solvates thereof.

Specific examples of compounds to be employed in the present method include:

- 10 (S)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetyl-amino)-butyric acid;
(R)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetyl-amino)-butyric acid;
(S)-2-Amino-4-dibenzofuran-2-yl-4-oxo-butyric acid;
(S)-2-Acetyl-amino-4-dibenzofuran-2-yl-4-oxo-butyric;
15 (S)-4-Dibenzofuran-2-yl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-4-oxo-butyric acid;
(S)-2-Benzoyl-amino-4-dibenzofuran-2-yl-4-oxo-butyric acid;
(S)-4-Dibenzofuran-2-yl-4-oxo-2-phenylacetyl-amino-butyric acid;
(S)-4-Dibenzofuran-2-yl-4-oxo-2-(3-phenyl-propionyl-amino)-butyric acid;
20 (S)-4-Dibenzofuran-2-yl-4-oxo-2-(7-phenyl-heptanoyl-amino)-butyric acid;
(S)-2-[(Biphenyl-4-carbonyl)-amino]-4-dibenzofuran-2-yl-4-oxo-butyric acid;
(S)-4-Dibenzofuran-2-yl-4-oxo-2-(dodecanoyl-amino)-butyric acid;
(S)-4-Dibenzofuran-2-yl-4-oxo-2-(dodecanoyl-amino)-butyric acid;
25 (S)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetyl-amino)-butyric acid;
(R)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetyl-amino)-butyric acid;
(S)-2-Amino-4-dibenzofuran-2-yl-4-oxo-butyric acid;
30 (S)-2-Acetyl-amino-4-dibenzofuran-2-yl-4-oxo-butyric acid;
(S)-4-Dibenzofuran-2-yl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-4-oxo-butyric acid;

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(L)-2-(Dibenzofuran-2-sulfonylamino)-propionic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-butyrac acid;
 (Dibenzofuran-2-sulfonylamino)-acetic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-succinic acid;
 5 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-tritylsulfanyl-propionic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-mercapto-propionic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-pentanoic acid

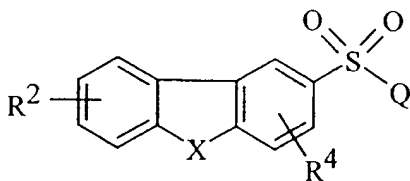
hydroxyamide;

(L)-2-(Dibenzofuran-2-sulfonylamino)-4-methyl-pentanoic acid;
 10 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-pentanoic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-phenyl-propionic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-propionic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-butyrac acid;
 (Dibenzofuran-2-sulfonylamino)-acetic acid;

15 (L)-2-(Dibenzofuran-2-sulfonylamino)-succinic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-tritylsulfanyl-propionic acid;
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-mercapto-propionic acid; and
 (L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-pentanoic acid

hydroxyamide.

20 Additional tricyclic sulfonamides are defined by the formula:



wherein Q is an un-natural amino acid;

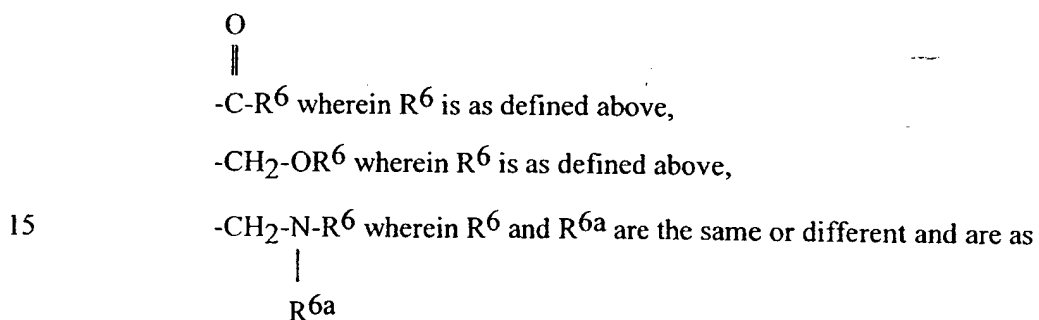
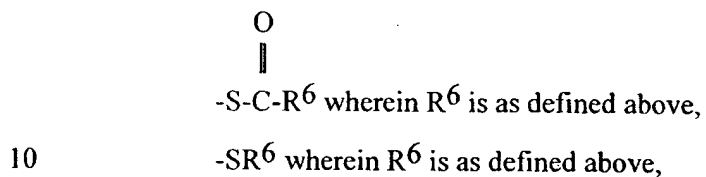
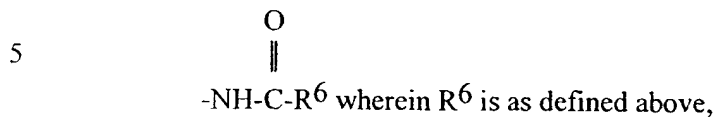
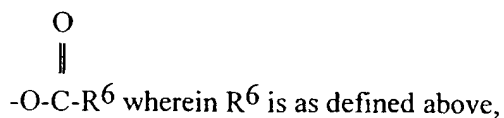
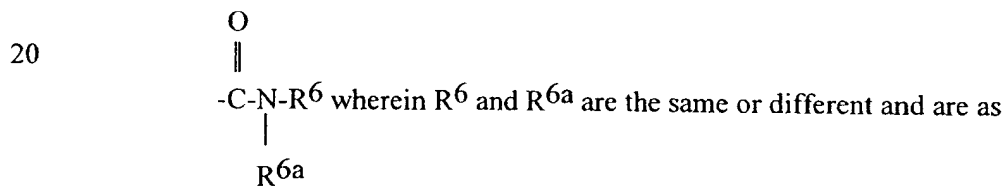
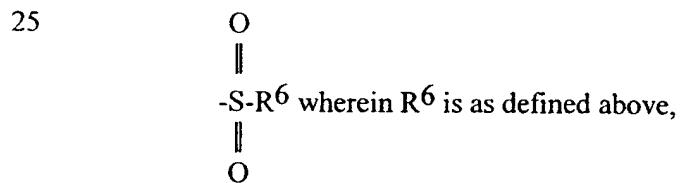
X is O, S, S(O)_n, CH₂, CO, or NH;

R² and R⁴ are independently hydrogen, C₁-C₅ alkyl, -NO₂, halogen, -OR⁵, -CN,

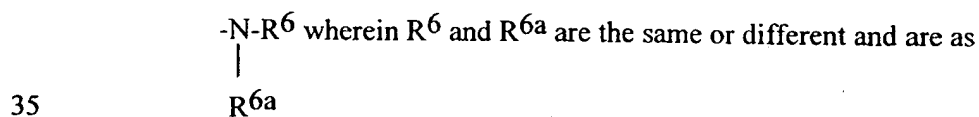
25 -CO₂R⁵, -SO₃R⁵, -CHO, -COR⁵, -CONR⁵R⁶, -(CH₂)_nNR⁵R⁶, -CF₃, or
 -NHCOR⁵;

each R⁵ and R⁶ are independently hydrogen or C₁-C₅ alkyl; and

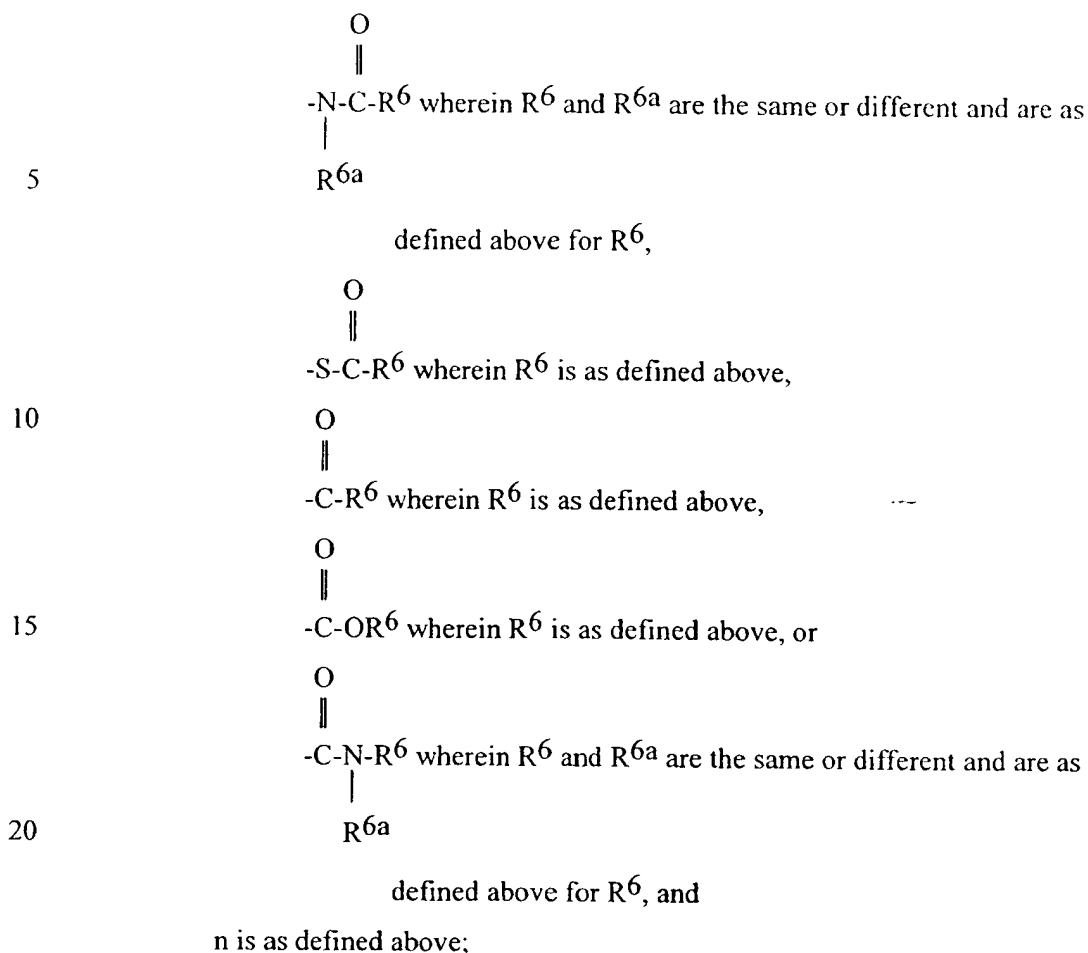
-93-

defined above for R^6 ,defined above for R^6 ,

30 cycloalkyl, or

heteroaryl, with the proviso that R and R^1 are not both hydrogen; R^2 is $-\text{OR}^6$ wherein R^6 is as defined above, ordefined above for R^6 ;

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R^5 is OH or SH; with the proviso that R^3 , R^{3a} , R^4 , and R^{4a} are hydrogen or at least one of R^3 , R^{3a} , R^4 , or R^{4a} is fluorine; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

Typical compounds from this class that are routinely utilized to treat atherosclerosis include:

- 4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;
- 4-(4'-Bromo-biphenyl-4-yl)-4-hydroxyimino-butyric acid;
- 30 4-(4'-Chloro-biphenyl-4-yl)-4-(dimethylhydrazono)-butyric acid;
- 4-(4'-Fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;
- (\pm)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxy-butyric acid;
- 4-(4'-Bromo-2'-fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;
- (\pm)-4-(4'-Chloro-biphenyl-4-yl)-3-fluoro-4-oxo-butyric acid;
- 35 4-(2',4'-Dichloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(4'-Chloro-biphenyl-4-yl)-2,2-difluoro-4-hydroxyimino-butyric acid;

and

4-(4'-Chloro-biphenyl-4-yl)-2,2,3,3-tetrafluoro-4-hydroxyimino-butyric acid.

5 A compound selected from the group consisting of:

4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(4'-Bromo-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(4'-Chloro-biphenyl-4-yl)-4-(dimethylhydrazono)-butyric acid;

4-(4'-Fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

10 (±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxy-butyric acid; —

4-(4'-Bromo-2'-fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

(±)-4-(4'-Chloro-biphenyl-4-yl)-3-fluoro-4-oxo-butyric acid;

4-(2',4'-Dichloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(2',4'-Difluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

15 (±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(3-phenylpropyl)-butyric acid;

(±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(2-phenylethyl)-butyric acid;

(±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(3-phthalimidopropyl)-butyric acid;

20 (±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(phenylthiomethyl)-butyric acid;

4-(4'-Chloro-2'-fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-Hydroxyimino-4-(4'-trifluoromethyl-biphenyl-4-yl)-butyric acid;

25 4-(4'-Chloro-biphenyl-4-yl)-4-methoxyimino-butyric acid;

(±)-4-(4'-Chloro-biphenyl-4-yl)-2-fluoro-2-[2-(1,3-dioxo-1,3-dihydro-isindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

(±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(1H-indol-3-yl)methyl-butyric acid;

30 (±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-methyl-butyric acid;

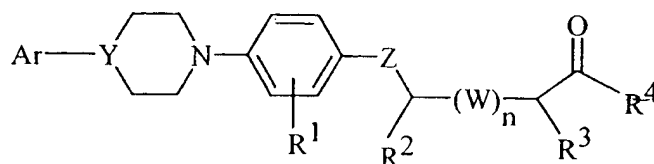
-99-

R^5 is hydrogen or C_1 - C_6 alkyl; and

R^6 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, phenyl, or substituted phenyl.

Specific compounds which can be employed include a compound of the above formula wherein R^1 is at the 4' position.

5 Another class of matrix metalloproteinase inhibitors useful in the present method are the heterocyclic substituted phenyl butyric acid derivatives, for example those defined by the formula:



Ar is selected from phenyl,

10 phenyl substituted with

alkyl,

NO_2 ,

halogen,

OR^5 wherein R^5 is hydrogen or alkyl,

15 CN,

CO_2R^5 wherein R^5 is as defined above,

SO_3R^5 wherein R^5 is as defined above,

CHO,

COR^5 wherein R^5 is as defined above,

20 $CONHR^5$ wherein R^5 is as defined above, or

$NHCOR^5$ wherein R^5 is as defined above,

2-naphthyl, or

heteroaryl;

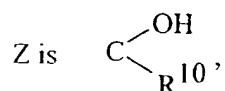
R^1 is selected from hydrogen,

25 methyl,

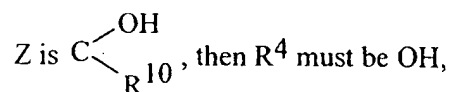
ethyl,

NO_2 ,

-101-



wherein R^{10} is as defined above for R^2 and R^3 , and is independently the same or different from R^2 and R^3 provided that when



5 $\text{C}=\text{O},$

$\text{C}=\text{NOR}^5$ wherein R^5 is as defined above, or

$\text{C}=\text{N}-\text{NR}^6\text{R}^{6a}$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^5 ;

W is $-\text{CHR}^5$ wherein R^5 is as defined above;

10 n is zero or an integer of 1;

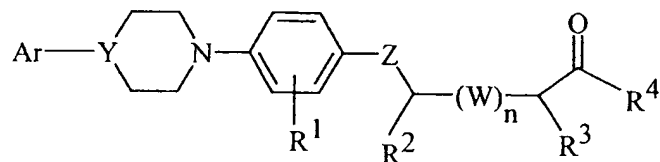
R^4 is OH,

NR^6R^{6a} wherein R^6 and R^{6a} are the same or different and are as defined above for R^5 , when R^4 is NR^6R^{6a} then Z must be $\text{C}=\text{O}$ or

NHOR^9 wherein R^9 is hydrogen, alkyl, or benzyl;

15 and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

Especially preferred MMP inhibitors have the formula



Ar is selected from phenyl,

phenyl substituted with

20 alkyl,

NO_2 ,

halogen,

OR^5 wherein R^5 is hydrogen or alkyl,

CN,

25 CO_2R^5 wherein R^5 is as defined above,

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$-(CH_2)_tNR^6R^{6a}$, wherein t is zero or an integer of from 1 to 9 and R^6 and R^{6a} are each the same or different and are as defined above for R^5 ,

$-(CH_2)_vSR^5$, wherein v and R^5 are as defined above,

$-(CH_2)_vCO_2R^5$, wherein v and R^5 are as defined above, or

$-(CH_2)_vCONR^6R^{6a}$, wherein R^6 and R^{6a} are the same or different and are as defined above for R^5 and v is as defined above;

10 R^3 is additionally $-(CH_2)_rR^7$ wherein r is an integer from 1 to 5 and R^7 is 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl, or 1,3-dihydro-1,3-dioxo-benzo[f]isoindol-2-yl;

Y is CH or N;

Z is $C \begin{smallmatrix} \text{OH} \\ \text{R}^{10} \end{smallmatrix}$,

15 wherein R^{10} is as defined above for R^2 and R^3 , and is independently the same or different from R^2 and R^3 provided that when

Z is $C \begin{smallmatrix} \text{OH} \\ \text{R}^{10} \end{smallmatrix}$, then R^4 must be OH,

$C=O$,

$C=NOR^5$ wherein R^5 is as defined above, or

20 $C=N-NR^6R^{6a}$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^5 ;

W is $-CHR^5$ wherein R^5 is as defined above;

n is zero or an integer of 1;

R^4 is OH,

25 NR^6R^{6a} wherein R^6 and R^{6a} are the same or different and are as defined above for R^5 , when R^4 is NR^6R^{6a} then Z must be $C=O$ or $NHOR^9$ wherein R^9 is hydrogen, alkyl, or benzyl;

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R^1 is hydrogen, methyl, $-\text{NO}_2$, $-\text{Cl}$, $-\text{NH}_2$, $-\text{NHCO}_2\text{CH}_3$, $-\text{OH}$, or $-\text{CO}_2\text{H}$;

R^2 and R^3 are the same or different and are independently selected from
 hydrogen, alkyl, $-(\text{CH}_2)_v\text{-aryl}$, $-(\text{CH}_2)_v\text{-heteroaryl}$, $-(\text{CH}_2)_v\text{-cycloalkyl}$,
 $-(\text{CH}_2)_p\text{-X}-(\text{CH}_2)_q\text{-aryl}$, $-(\text{CH}_2)_p\text{-X}-(\text{CH}_2)_q\text{-heteroaryl}$, $-(\text{CH}_2)_t\text{NR}^6\text{R}^{6a}$,
 5 $-(\text{CH}_2)_v\text{R}^7$, $-(\text{CH}_2)_v\text{CO}_2\text{R}^5$, $-(\text{CH}_2)_v\text{CONR}^6\text{R}^{6a}$, or $-(\text{CH}_2)_v\text{SR}^5$;

m is zero or 1;

Y is CH or N; provided that when $m = 1$, Y does not = N;

z is zero or 1;

W is $-\text{CHR}^8$;

10 n is zero or 1;

R^4 is $-\text{OH}$, $-\text{NR}^6\text{R}^{6a}$, or $-\text{NHOR}^9$;

R^5 is hydrogen or alkyl;

v is 1 to 5;

X is O or S;

15 p and q are independently 1 to 5, provided that $p + q$ is not greater than 5;

t is 1 to 9;

R^6 and R^{6a} are each the same or different and are hydrogen or alkyl;

R^7 is 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl, or 1,3-dihydro-1,3-dioxo-
 benzo[f]isoindol-2-yl;

20 R^8 is hydrogen or alkyl; and

R^9 is hydrogen, alkyl, or benzyl; or

a pharmaceutically acceptable salt thereof.

Specific sulfonamide derivatives to be employed in the present method
 include:

25 [4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetic acid;

N-Hydroxy-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-
 acetamide;

3-[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-(4-Hydroxy-phenyl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperazin-1-yl)-benzenesulfonylamino]-propionic acid;

5 (S)-2-{4-[4-(3-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(S)-2-{4-[4-(3-Hydroxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid hydrobromide;

(S)-2-{4-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

10 (R)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

15 (S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

20 [4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetic acid;

N-Hydroxy-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetamide;

3-[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

25 (R)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

30 (R)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-2-{4-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(R)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

5 (S)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid; and

10 (S)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid.

Additional specific compounds which can be used include:

2-(Dibenzofuran-2-sulfonylamino)-3-(4-fluoro-phenyl)-propionic acid;

15 2-(Dibenzofuran-2-sulfonylamino)-3-phenyl-propionic acid;

3-(4-tert-Butoxy-phenyl)-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

(Dibenzofuran-2-sulfonylamino)-phenyl-acetic acid;

3-tert-Butoxy-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

20 2-(Dibenzofuran-2-sulfonylamino)-3-(1H-imidazol-4-yl)-propionic acid;

2-(Dibenzofuran-2-sulfonylamino)-3-hydroxy-propionic acid;

3-Benzoyloxy-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

6-Benzoyloxycarbonylamino-2-(dibenzofuran-2-sulfonylamino)-hexanoic acid;

25 5-Benzoyloxycarbonylamino-2-(dibenzofuran-2-sulfonylamino)-pentanoic acid;

(Dibenzofuran-2-sulfonylamino)-(4-methoxy-phenyl)-acetic acid;

3-Chloro-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

3-(4-Benzoyloxy-phenyl)-2-(dibenzofuran-2-sulfonylamino)-propionic

30 acid;

2-(Dibenzofuran-2-sulfonylamino)-5-p-tolyl-sulfonylamino-pentanoic acid;

2-(Dibenzofuran-2-sulfonylamino)-4-mercapto-butyric acid;

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- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(pyridin-4-ylsulfonyl)-
acetylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(2,4-dichloro-phenoxy)-
acetylamino]-hexanoic acid;
- 5 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-thiophen-2-yl-
acetylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(3-phenyl-acryloylamino)-
hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(7-phenyl-heptanoylamino)-
10 hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(2-trifluoromethyl-phenyl)-
acetylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-phenoxy-butyrylamino)-
hexanoic acid;
- 15 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-phenyl-sulfonyl-
acetylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-phenoxy-acetylamino)-
hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(3,4-dimethoxy-phenyl)-
20 acetylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-tert-butyl-phenoxy)-
acetylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[3-(3,4-dimethoxy-
phenyl)-propionylamino]-hexanoic acid;
- 25 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-cyclopent-1-enyl-
acetylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-methoxy-phenoxy)-
acetylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(naphthalen-1-yloxy)-
30 acetylamino]-hexanoic acid;

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- 6-(2-Benzo[1,3]dioxol-5-yl-acetylamino)-2-(4'-bromo-biphenyl-4-sulfonylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-pyridin-2-yl-acetylamino)-hexanoic acid;
- 5 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[4-(4-nitro-phenyl)-butyrylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-tert-butyl-phenoxy)-acetylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[3-(3,4-dimethoxy-phenyl)-propionylamino]-hexanoic acid;
- 10 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-cyclopent-1-enyl-acetylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-methoxy-phenoxy)-acetylamino]-hexanoic acid;
- 15 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(4-phenyl-butyrylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[4-(4-chloro-3-methyl-phenoxy)-butyrylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-chloro-phenyl)-propionylamino]-hexanoic acid;
- 20 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-methoxy-phenyl)-propionylamino]-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-pyridin-3-yl-acetylamino)-hexanoic acid;
- 25 6-(2-Benzo[1,3]dioxol-5-yl-acetylamino)-2-(4'-bromo-biphenyl-4-sulfonylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-(2-naphthalen-1-yl-acetylamino)-hexanoic acid;
- 2-(4'-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-chloro-phenoxy)-propionylamino]-hexanoic acid;
- 30

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N⁴-Hydroxy-2R-isobutyl-N¹-(1S-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethylcarbamoyl}-2,2-dimethyl-propyl)-3S-(thiophen-2-yl-sulfanylmethyl)-succinamide;

5 N¹-(1S-[2,2-Di-(methoxymethyl)-propylcarbamoyl]-2,2-dimethyl-propyl)-N⁴-hydroxy-3R-isobutyl-3S-(thiophen-2-yl-sulfanylmethyl)-succinamide;

N⁴-Hydroxy-2R-isobutyl-N¹-(1S-[2-(2-methoxy-ethoxy)-ethylcarbamoyl]-2,2-dimethyl-propyl)-3S-propyl-succinamide;

10 N⁴-(1S-Cyclobutylcarbamoyl-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-(1S-Cyclopentylcarbamoyl-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

15 N⁴-(1S-Cyclohexylcarbamoyl-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-(1S-Cycloheptylcarbamoyl-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

20 N⁴-(1S-Cyclopropylcarbamoyl-2-mercapto-2-methyl-propyl)-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-(3-phenyl-propenyl)-succinamide;

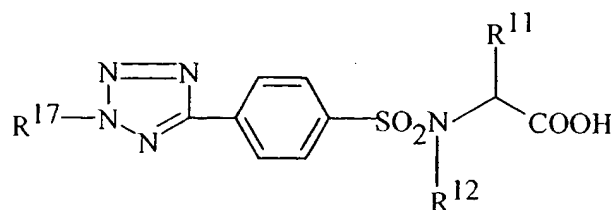
N⁴-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-(3-phenyl-propyl)-succinamide;

25 N⁴-[2,2-Dimethyl-1S-(2-phenyl-cyclopropylcarbamoyl)-propyl]-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

2S-Allyl-N⁴-(1-cyclopropylcarbamoyl-2,2-dimethyl-propyl)-N¹-hydroxy-3R-isobutyl-succinamide;

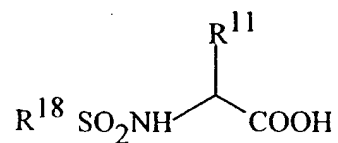
30 2S-Allyl-N⁴-(1S-cyclopropylcarbamoyl-2-mercapto-2-methyl-propyl)-N¹-hydroxy-3R-isobutyl-succinamide;

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where R^{11} and R^{12} are as defined above, and R^{17} is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

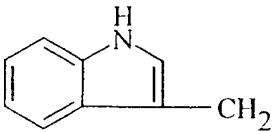
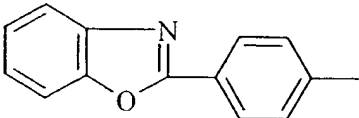
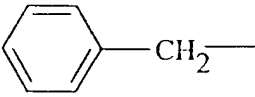
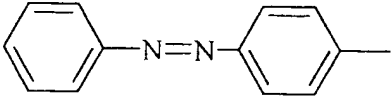
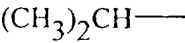
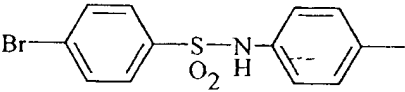
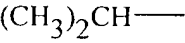
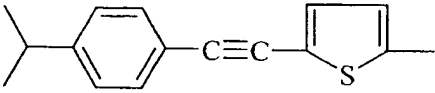
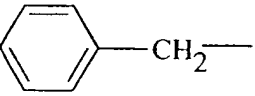
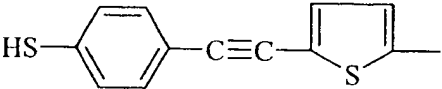
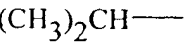
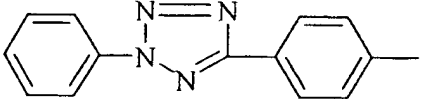
Especially preferred are compounds of the formula



5

wherein R^{11} and R^{18} are as follows:

R^{11}	R^{18}

R11	R18
	
	
	
	
	
	

The following patents and applications covering MMP inhibitors are incorporated herein by reference: United States 5,753,653; WO 96/16027; WO 97/20824; WO 98/50348; WO 98/43963; WO 9832748; WO 98/17643; and EP 0780386. These include compounds such as shown below.

4-[2-(2-Carboxymethyl-4-phenyl-butylamino)-3-cyclohexylpropionylamino]benzoic acid methyl ester;

4-[2-(2-Carboxymethyl-4-phenyl-butyrylamino)-3,3-methyl-butyrylamino]-benzoic acid methyl ester;

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- 4-[2-(2-Hydroxaminocarbonylmethyl-4-methyl-pentanoylamino)-3-(1H-indol-3-yl)-propionylamino]-benzoic acid methyl ester;
- 3-[2-(4-Methoxy-benzylsulfanyl)-2-methyl-1-phenylcarbamoyl-propylcarbamoyl]-5-methyl-hexanoic acid;
- 5 3-[2-(4-Methoxy-benzylsulfanyl)-2-methyl-1-phenylcarbamoyl-propylcarbamoyl]-5-methyl-hexanoic acid N-hydroxyamide;
- 4-[2-(2-Hydroxaminocarbonylmethyl-4-methyl-pentanoylamino)-2-cyclohexyl-acetyl-amino]-benzoic acid methyl ester;
- 2-(Phenyl-2-ethyl)benzoic acid N-hydroxy amide;
- 10 4-[2-(2-Acylhydrazinomethyl-4-methyl-pentanoylamino)-3-(1H-indol-3-yl)-propionylamino]-benzoic acid methyl ester;
- 2-(Propylthio)-pyridine-3-N-(hydroxy)carboxamide;
- 4-[2-(2-Carboxymethyl-5-phenyl-pentanoylamino)-2-cyclohexylacetyl-amino]benzoic acid methyl ester;
- 15 [4-(N-Hydroxyamino)-2R-isobutyl-3S-((thien-2-ylthio)methyl)succinyl]-L-phenylalanine-N-methylamide;
- N-Hydroxy-5-phenylpentanamide;
- 4-[2-(2-Carboxymethyl-5-(3-hydroxyphenyl)-valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 20 4-[2-(2-Carboxymethyl-5-(3-hydroxyphenyl)-4-pentenoyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 4-[2-(2-Carboxymethyl-5-(3-aminophenyl)-4-pentenoyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester, trifluoroacetate salt;
- 2-(Phenyl-2-ethyl)pyridine-3-N-hydroxycarboxamide;
- 25 4-[2-(2-Carboxymethyl-5-(3-aminophenyl)-valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 4-[2-(2-Carboxymethyl-5-(3-aminophenyl)acetyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 4-[2-(2-Carboxymethyl-5-(3-aminophenyl)acetyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 30 2-[3-(3-Hydroxy-phenyl)-propyl]-benzohydroxamic acid;
- 2-(Thiobenzyl)benzoic acid N-hydroxy amide;
- 1-(3-Phenyl-propyl)-pyrrolidine-2-hydroxamic acid;

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- 4-[2-(2-Carboxymethyl-5-(biphen-4-yl)-valeroyl)amino)-4-methyl-
valeroyl]aminobenzoic acid methyl ester;
cis-4-Benzylsulfanyl-pyrrolidine-2-carboxylic acid;
2-Cyclohexylmethyl sulfonyl-benzoic acid;
5 Pyrrolidine-1-carbothioic acid phenethyl-amide;
3-(2-Methyl-thiazol-4-yl)-N-phenethyl-propionamide;
N-Phenyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-
propionamide;
3-(3H-Imidazol-4-yl)-N-phenethyl-propionamide;
10 4-[2-(2-Carboxymethyl-5-(formamido)valeroyl)amino)-4-methyl-
valeroyl]aminobenzoic acid methyl ester;
2-Cyclohexylmethyl sulfonyl-benzohydroxamic acid;
[2-Oxo-3-(3-phenyl-propyl)-tetrahydro-furan-3-yl]-acetic acid;
4-[2-(2-Carboxymethyl-5-(fluoren-2-yl)valeroyl)amino)-4-methyl-
15 valeroyl]aminobenzoic acid methyl ester;
4-[2-(2-Carboxymethyl-2-(3-thienyl)acetyl-amino)-4-methyl-
valeroyl]aminobenzoic acid methyl ester;
4-[2-(2-Benzylthio-3-carboxy-propionyl-amino)-4-methylpentanoyl-amino]-
benzoic acid methyl ester;
20 4-[2-(2-Carboxymethyl-4-(2-indolyl)butyryl-amino)-4-methyl-
valeroyl]aminobenzoic acid methyl ester;
1-Allyl-3-(2-hydroxyethyl)-2-thiourea;
3-(1-Hydroxyimino-propyl)-6-phenyl-hexanoic acid;
2-(3H-Imidazol-4-ylmethyl)-N 1,N 4-diphenethyl-succinamide;
25 3-(2-Hydroxymethyl-3H-imidazol-4-yl)-N-phenethyl-propionamide;
6-Phenyl-3-propionyl-hexanoic acid;
4-{2-([2-Hydroxyamino-2-hydroxyimino-ethyl]-5-phenyl-
pentanoyl-amino)-4-methyl-pentanoyl-amino}-benzoic acid methyl ester;
4-[2-(2-(2-Phenylcyclopropyl)succinyl-amino)-4-methyl-
30 valeroyl]aminobenzoic acid methyl ester;
6-Biphenyl-4-yl-[2,2-dimethyl-1-(pyridin-4-ylcarbamoyl)-
propylcarbamoyl]-hexanoic acid trifluoroacetate salt;

- [3-(3-Biphenyl-4-yl-propyl)-2-oxo-pyrrolidin-3-yl]-acetic acid;
 2-Benzylsulfonyl-cyclopent-1-ene-carboxylic acid hydroxamide;
 [2-Oxo-3-(3-phenyl-propyl)-pyrrolidin-3-yl]-acetic acid;
 [3-(3-Naphthalen-2-yl-propyl)-2-oxo-pyrrolidin-3-yl]-acetic acid;
 5 2-Benzylsulfonyl-cyclohex-1-enecarboxylic acid hydroxy amide;
 6-Benzylsulfonyl-cyclohex-1-enecarboxylic acid hydroxy amide;
 2R-(3-(4-Biphenyl)propyl)-N-(3-methylpyridine)succinamide;
 {3-[3-(3-Hydroxy-phenyl)-propyl]-2-oxo-pyrrolidin-3-yl}-acetic acid;
 6-Biphenyl-4-yl-{{cyclohexyl-(3-morpholin-4-yl-propylcarbamoyl)-
 10 methyl]-carbamoyl}hexanoic acid;
 [2-Oxo-3-(3-biphenyl-propyl)-tetrahydro-furan-3-yl]-acetic acid;
 4-[2-(2-Thioamidomethyl-5-phenyl-valeryl-amino)-4-methyl-
 valeroylamino]-benzoic acid methyl ester;
 4-[2-(2-Amino-2-hydroxyimino-ethyl-5-phenyl-valeryl-amino)-4-methyl-
 15 valeroylamino]-benzoic acid methyl ester;
 6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(4-methylsulfamoyl-
 phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;
 6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(2-hydroxyethylsulfamoyl-
 phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;
 20 1-(N-Hydroxy)-3-(2-bibenzyl)urea;
 4-(2-{5-[7-(2-Amino-acetyl-amino)-9H-fluoren-2-yl]-2-carboxymethyl-
 pentanoylamino}-4-methyl-pentanoylamino)-benzoic acid methyl ester TFA salt;
 3R-(6-(4-Biphenyl)propyl)-N-(3-methylpyridinecarbamoyl)-hexanoic acid
 N-hydroxy amide;
 25 6-Biphenyl-4-yl-3-[cyclohexyl-(4-(2-hydroxy-ethylsulfamoyl)-
 phenylcarbamoyl)-methylcarbamoyl]-hexanoic acid;
 6-Biphenyl-4-yl-3-[cyclohexyl-(4-(2-dimethylamino-ethylsulfamoyl)-
 phenylcarbamoyl)-methylcarbamoyl]-hexanoic acid, trifluoroacetate salt;
 4-(2-{2-Carboxymethyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-pentanoylamino}-
 30 4-methyl-pentanoylamino)-benzoic acid methyl ester;
 4-[2-(2-Carboxymethyl-5-(4-(2-hydroxy-ethyl)-phenyl)-pentanoylamino)-
 4-methyl-pentanoylamino]-benzoic acid methyl ester;

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- 6-Biphenyl-4-yl(2-hydroxy-2-methyl-1-phenylcarbamoyl-propylcarbamoyl)-hexanoic acid;
- 3-{2-Allylsufamyl-2-methyl-1-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-propylcarbamoyl}-6-biphenyl-4-yl-hexanoic acid;
- 5 4-[2-(5-Biphenyl-4yl-2-carboxymethyl-pentanoylamino)-4,5-dihydroxy-pentanoylamino]-benzoic acid methyl ester;
- 4-(2-{5-[4'-(2-Amino-ethoxy)-biphenyl-4-yl]-2-carboxymethyl-pentanoylamino}-4-methyl-pentanoylamino)-benzoic acid methyl ester;
- 6-Biphenyl-4-y-3-(R)-(2-hydroxy-1-(S)-phenyl-ethylcarbamoyl)-hexanehydroxamic acid;
- 10 3-(R)-(1-(R)-Benzyl-2-hydroxy-ethylcarbamoyl)-6-biphenyl-4-yl-hexanehydroxamic acid;
- N-[5-(Biphenyl-4-yl)-2-(N-hydroxyformamido)methylpentanoyl]-tert-leucine, N-(pyrid-4-yl)amide;
- 15 [3-(3-Naphthalen-2-yl-propyl)-2-oxo-tetrahydro-furan-3-yl]-acetic acid;
- 6-Biphenyl-4-yl-3-(R)-(2-hydroxy-1-hydroxymethyl-ethylcarbomyl)-hexanehydroxamic acid;
- 4-[2-(2-Carboxymethyl-5-naphthalen-2-yl-pentanoylamino)-4-methyl-pentanoylamino]-benzoic acid methyl ester;
- 20 3-[2,2-Dimethyl-1-(pyridin-4-ylcarbamoyl)-propylcarbamoyl]-5-methyl-hexanoic acid;
- N1-[2,2-Dimethyl-1-(pyridin-4-ylcarbamoyl)-propyl]-N4-hydroxy-2-isobutyl-succinamide;
- 4-{2-[2-Carboxymethyl-5-(2-fluoro-biphenyl-4-yl)-pentanoylamino]-4-methyl-pentanoylamino}-benzoic acid methyl ester;
- 25 6-Biphenyl-4-yl-3(R)-(1(S)-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-hexanoic acid;
- 4-{2-[5-Biphen-4-yl-2-(1-carboxy-ethylamino)-pentanoylamino]-4-methyl-pentanoylamino}-benzoic acid methyl ester;
- 30 6-Biphenyl-4-yl-3(R)-(1(S)-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-hexanehydroxamic acid;

- 3-(R)-(2-(R)-Benzyloxy-1-(S)-hydroxymethyl-propylcarbamoyl)-6-biphenyl-4-yl-hexanoic acid;
- 4-[4-Methyl-2-(2-nitromethyl-5-phenyl-pentanoylamino)-pentanoylamino]-benzoic acid methyl ester;
- 5 6-Biphenyl-4-yl-3-[3-methyl-1-(4-(2-hydroxyethylsulfamoyl)-phenylcarbamoyl)-butylcarbamoyl]-hexanoic acid;
- 6-Biphenyl-4-yl-3-(1-hydroxymethyl-2-phenyl-ethylcarbamoyl)-hexanoic acid;
- N1-(1-Benzyl-2-hydroxy-ethyl)-2-(3-biphenyl-4-yl-propyl)-N4-hydroxy-succinamide;
- 10 6-Biphenyl-4-yl-3-(R)-(1-hydroxymethyl-2-(S)-(1H-imidazol-4-yl)-ethylcarbamoyl)-hexanehydroxamic acid;
- N-Hydroxy-2-[2-Oxo-3-(3-phenyl-propyl)-tetrahydro-furan-3-yl]-acetamide;
- 15 4-[2-(2-Carboxymethyl-5-(2-hydroxy-biphen-4-yl)-valeroylamino)-4-methyl-valeroylamino]-benzoic acid methyl ester;
- N1-(2-Benzyloxy-1-hydroxymethyl-propyl)-2-(3-biphenyl-4-yl-propyl)-N4-hydroxy-succinamide;
- trans-2-(4-Phenoxy-benzylsulfanyl)-cyclohexancarboxylic acid
- 20 hydroxamide;
- 2-(4-Indol-1-yl-benzylsulfanyl)-cyclohexancarboxylic acid hydroxamide;
- 6-Biphenyl-4-yl-3-[2-hydroxy-2-methyl-1-(4S-methylsulfinyl)-phenylcarbamoyl]-propylcarbamoyl]-hexanoic acid;
- 6-Biphenyl-4-yl-3-(2,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-3-ylcarbamoyl)-hexanoic acid;
- 25 5-Biphenyl-4-yl-2-[(formyl-hydroxy-amino)-methyl]-pentanoic acid{1-[4-(2-dimethylamino-ethylsulfamoyl)-phenylcarbamoyl]-3-methyl-butyl}-amide;
- 2-(3-Biphenyl-4-yl-propyl)-N4-hydroxy-N1-(2,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-3-yl)-succinamide;
- 30 6-Biphenyl-4-yl-3-(2,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-3-ylcarbamoyl)-hexanoic acid;

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3-(R)-(2-Hydroxy-1-(S)-(1H-imidazol-4-yl)-ethylcarbamoyl)-6-(4-(2-methyl-thiazol-4-yl)-phenyl)-hexanoic acid;

3-(R)-(2-Hydroxy-1-(S)-(1H-imidazol-4-yl)-ethylcarbamoyl)-6-(4-(2-methyl-thiazol-4-yl)-phenyl)-hexanehydroxamic acid;

5 5-Biphenyl-4-yl-2-(1-hydroxymethyl-3-methylsulfanyl-propylcarbamoyl)-pentanoic acid;

2-(3-Biphenyl-4-yl-propyl)-N-hydroxy-N'-(1-hydroxymethyl-3-methylsulfanyl-propyl)malonamide;

6-Biphenyl-4-yl-3-(3-hydroxy-piperidine-1-carbonyl)-hexanoic acid;

10 6-Biphenyl-4-yl-3-(3-hydroxy-piperidine-1-carbonyl)-hexanoic acidhydroxamide;

1-(4-Methoxy-benzenesulfonyl)-piperidine-2-carboxylic acid hydroxamide;

15 1-[4-Bromo-phenoxy]-benzenesulfonyl)-piperidine-2-carboxylic acid hydroxamide;

N-(1-Benzyl-2-methoxy-ethyl)-3-(3-biphenyl-4-yl-pyrrol-1-yl)-succinamic acid;

N-(1-Benzyl-2-methoxy-ethyl)-3-(3-biphenyl-4-yl-pyrrol-1-yl)-succinamic hydroxamic acid;

20 6-Biphenyl-4-yl-3(R)-2(S)-hydroxy-(1(S)-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-hexanoic acid;

3-(1-Benzyl-2-hydroxy-ethylcarbamoyl)-5-methyl-hexanoic acid;

N¹-(1-benzyl-2-hydroxy-ethyl)-N⁴-hydroxy-2-isobutyl-succinamide;

25 6-Biphenyl-4-yl-3(R)-2(S)-hydroxy-(1(S)-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-hexanoic hydroxamic acid;

1-[4-Bromo-phenoxy]-benzenesulfonyl)-piperidine-2-carboxylic acid;

6-Biphenyl-4-yl-3-(2-hydroxy-1-hydroxymethyl-propylcarbamoyl)-hexanoic acid;

6-Biphenyl-4-yl-3-(R)-(2-oxo-cyclohexyl-1-(S)-carbamoyl)-hexanoic acid;

30 6-Biphenyl-4-yl-3-(2-hydroxy-1-hydroxymethyl-propylcarbamoyl)-hexanoic hydroxamic acid;

- 6-Biphenyl-4-yl-3-(R)-(2-oxo-1-tetrahydrofuran-3-(S)-ylcarbamoyl)-hexanoic acid;
- 3-[2,2-Dimethyl-1-(pyridin-4-ylcarbamoyl)-propylcarbamoyl]-2-hydroxy-5-methyl-hexanoic acid-hydrochloride salt;
- 5 N⁴-(2,2-Dimethyl-1-methylcarbamoyl-propyl)-2,N¹-dihydroxy-3-isobutyl-succinamide;
- 6-Biphenyl-4-yl-3-(R)-(2-oxo-azepan-3-(S)-ylcarbamoyl)-hexanoic acid;
- N-(1-Benzyl-2-hydroxy-ethyl)-3-(4-biphenyl-4-yl-pyrazol-1-yl)-succinamic acid;
- 10 N-(8-Oxo-4-oxa-1,7-diaza-tricyclo[9.6.1.0 12,17]octadeca-11(18),12(17),13,15-tetraen-9R-yl)-3S-(3-phenyl-pyrrol-1-yl)-succinamic acid;
- 4-Acetyl-1-[4-phenoxy-benzenesulfonyl]-piperazine-2-carboxylic acid, N-hydroxyamide;
- 1-(Diphenylphosphinic)-piperidine-2-carboxylic acid hydroxamide;
- 15 3R-(3-Biphenyl-4-yl-pyrrol-1-yl)-N-[3S-(2RS-hydroxy-5-methyl)-hexyl]-succinamic acid;
- N-(1-(S)-Benzyl-2-hydroxy-ethyl)-3-(R)-(2-biphenyl-4-yl-cyclopropylmethyl)-succinamic acid;
- 6-Biphenyl-4-yl-3-(R)-(2-oxo-1-tetrahydrofuran-3-(S)-ylcarbamoyl)-hexanehydroxamic acid;
- 20 1-[4-(4-Bromo-phenoxy)-benzenesulfonyl]-4-methyl-piperazine-2-carboxylic acid N-hydroxyamide;
- 4-(4-Methoxy-benzenesulfonyl)-thiomorpholine-3-carboxylic acidhydroxyamide;
- 25 3-(Diphenylphosphinic)-propanoic acid;
- 3-(Diphenylphosphinic)-propanoic acid hydroxyamide;
- 4-[2-(2-Carboxymethyl-5-(4-(3-hydroxy-propyl)-phenyl)-pentanoylamino)-4-methyl-pentanoylamino]-benzoic acid methyl ester;
- 1-[4-(4-Chlorophenoxy)benzenesulfonyl]-N-hydroxy-4-(N-methylcarbamoyl)piperazine-2-carboxamide;
- 30 4-[4-(4-Bromo-phenoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid N-hydroxyamide;

- 4-(4-(4-Chlorophenoxy)benzenesulfonyl)-N-hydroxy-morpholine-3R-carboxamide;
- 2S-[1R-(3-(4'-Cyano-biphenyl-4-yl)-pyrrol-1-yl)-N-(2,2-dimethyl-1S-hydroxymethylpropylcarbamoyl)-methyl]]-pentanoic acid;
- 5 2(S,R)-{1S-Benzyl-2-hydroxyethylcarbamoyl-[3R-(4'-cyano-biphenyl-4-yl)-pyrrol-1-yl]-methyl} pentanoic acid;
- 2S-[3-(Biphenyl-4-yl)-pyrrol-1R-yl-(1S-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-methyl]-5-hydroxypentanoic acid;
- 10 1-(1,3-Dihydro-isoindole-2-sulfonyl)-piperidine-2-carboxylic acid hydroxamide;
- 3-[3-(4'-Carbamoyl-biphenyl-4-yl)-pyrrol-1-yl)-N-(1-hydroxymethyl-2,2-dimethyl-propyl)-succinamic acid;
- 4-Methyl-1-(4-(4-chlorophenyl)benzenesulfonyl)-N-hydroxy-2R-piperazinecarboxamide hydrochloride;
- 15 1-[4-Chlorophenoxybenzenesulfonyl]-N-hydroxy-2R-piperazinecarboxamide;
- 2-(3-Phenyl-propylsulfonyl)-cyclohexane carboxylic acid hydroxamide;
- 1-(Pyrolidine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;
- 1-(Piperidine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;
- 20 4-[4-Bromo-phenoxy-benzenesulfonyl]-oxothiomorpholine-3-carboxylic acid-N-hydroxyamide;
- 1-[4-(4-Methoxy-phenylsulfonyl)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;
- 1-[4-(4-Nitrile-phenoxy)-benzenesulfonyl]-4-(tert-butoxycarbonyl)-piperazine-2-carboxylic acid N-hydroxyamide;
- 25 2S-[3-(Biphenyl-4-yl)-pyrrol-1R-yl-(1S-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-methyl]-pent-4-enoic acid;
- 6-Oxo-3-(4-phenoxy-benzenesulfonyl)-hexahydro-pyrimidine-4-carboxylic acid hydroxamate;
- 30 4-(t-Butoxycarbonyl)-1-(4-(pyridin-2-yl)oxybenzenesulfonyl)-N-hydroxy-piperazine-2-carboxamide;

- N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-(3-phenyl-pyrrol-1-yl)-succinamic acid;
- 3R-(3-Biphenyl-4-yl)-N-(2-hydroxy-1S-hydroxymethyl-2-methyl-propyl)-succinamic acid;
- 5 1-(Pyrrolidine-1-carbonyl)-pyrrolidine-2(R)-carboxylic acid;
- 1-(Pyrrolidine-1-carbonyl)-pyrrolidine-2(R)-carboxylic acid hydroxyamide;
- 1-Phenethylcarbamoyl-pyrrolidine-2(R)-carboxylic acid;
- R-4-[4-(Bromophenoxy)-benzenesulfonyl]-2,2-dimethyl-1-oxo-thiomorpholine-3-carboxylic acid hydroxyamide;
- 10 4-(Ethoxycarbonyl)methyl-1-(4-(4-chlorophenyl)benzenesulfonyl)-N-hydroxy-2R-piperazinecarboxamide hydrochloride;
- N-(2R-Hydroxy-indan-1R-yl)-3R-[3-(4-pyridin-4-yl-phenyl)-pyrrol-1-yl]-succinamic acid;
- N-(4,4-Dimethyl-2-oxo-tetrahydro-furan-3S-yl)-3R-[3-(4-pyridin-4-yl-phenyl)-pyrrol-1-yl]-succinamic acid;
- 15 N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-[3-(4-pyridin-4-yl-phenyl-4-yl)-pyrrol-1-yl]-succinamic acid;
- 1-Phenethylcarbamoyl-pyrrolidine-2(R)-carboxylic acid hydroxyamide;
- N-(2,2-Dimethyl-1S-methyl carbamoyl-propyl)-3R-[3-(4-propyl-phenyl)-pyrrol-1-yl]-succinamic acid;
- 20 1-(4-Benzyl-piperazine-1-sulfonyl)-piperdine-2-carboxylic acid hydroxyamide;
- 3(S)-N-hydroxy-4-(4-(pyridin-4-yl)oxybenzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide;
- 25 2(R)-4-Methyl-1-(4-(4-fluorophenyl)benzenesulfonyl)-N-hydroxy-piperazine-2-carboxamide;
- N-(2,2-Dimethyl-1-methylcarbamoyl-propyl)-3-(5-biphenyl-4-yl-furan-2-yl)-succinamic acid;
- N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-(3-pyridin-4-yl-pyrrol-1-yl)-succinamic acid;
- 30 1-((2-Pyridyl)-4-piperazine-1-sulfonyl)-piperdine-2-carboxylic acid hydroxyamide;

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- 3-[3-(4'-Cyano-biphenyl-4-yl)-pyrrol-1-yl]-N-(2,2-dimethyl-1-methylcarbamoyl-propyl)-succinamic acid;
- 2-(2-Biphenyl-4-yl-ethylsulfonyl)-cyclohex-1-ene-carboxylic acid hydroxyamide;
- 5 6-(2-Biphenyl-4-yl-ethyl sulfonyl)-cyclohex-1-ene-carboxylic acid hydroxyamide;
- N-(4-Pyridin-4-yl-oxy-benzenesulfonyl)-3,3-dimethyl-S-(benzylthio)-D-cysteine;
- 3-[3-4'-Carbamoyl-biphenyl-4-yl)-pyrrol-1-yl]-N-[2,2-dimethyl-1-(pyridin-4-yl-carbamoyl)-propyl]-succinamic acid;
- 10 N-(4-Phenoxy-benzenesulfonyl)-3,3-dimethyl-S-(methylthio)-D-cysteine, N-hydroxyamide;
- 1-(4-Phenoxy-piperidine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;
- 15 3(R)-4-[4-(4-Bromo)phenoxybenzenesulfonyl]-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid;
- N-(4-[4-Chloro-phenoxy]-benzenesulfonyl)-3,3-dimethyl-S-(methylthio)-D-cysteine;
- N-(4-[4-Chlorophenoxy]-benzenesulfonyl)-3,3-dimethyl-S-(methylthio)-D-cysteine, N-hydroxyamide;
- 20 N-(4-[4-Chlorophenoxy]-benzenesulfonyl)-3,3-dimethyl-S-(methylsulfoxy)-D-cysteine, N-hydroxyamide;
- 2(R)-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-3-methyl-3-(pyridin-2-ylsulfanyl)-butyric acid;
- 25 2(R)-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-3-methyl-3-(pyridin-3-ylsulfanyl)-butyric acid;
- 2(R)-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-3-methyl-3-(pyridin-4-ylsulfanyl)-butyric acid;
- cis-2-(2-Phenyl-ethanesulfonyl)-cyclohexanecarboxylic acid hydroxyamide;
- 30 3(R)-N-Hydroxy-4-(4-(imidaz-1-yl)phenoxybenzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide;

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2(R)-[4-(4-Fluoro-phenoxy)benzenesulfonylamino]-3-methyl-3-(pyridin-2-yl-sulfonyl)-butyric acid, hydroxyamide;

3(R)-N-Hydroxy-4-(4-((pyridin-4-yl)methyl)oxybenzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide;

5 1-[4-(4-Chloro-phenoxy)-benzenesulfonyl]-4-(1-methyl-1H-imidazole-4-sulfonyl)-piperazine-2-carboxylic acid hydroxamide;

N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-[1-(4'-cyanobiphenyl-4-yl)-1H-pyrrol-3-yl]-succinamic acid;

3-Carboxymethylsulfanyl-2-(4-(4-fluoro-phenoxy)-
10 benzenesulfonylamino)-3-methyl-butyric acid:

2,2-Dimethyl-1-oxo-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-1S14-thiomorpholine-3-carboxylic acid hydroamide;

1-[4-(Pyridin-2-yl)sulfanyl]-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

15 2(R)-[4-(4-(fur-3-yl)-phenoxy)-benzenesulfonylamino]-3-methyl-3-(pyridin-4-yl-sulfanyl)-butyric acid;

2,2-Dimethyl-1-oxo-4-[4-(pyridin-4yloxy)-benzenesulfonyl]-1S14-thiomorpholine-3-carboxylic acid hydroamide;

20 {2-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-2-hydroxycarbamoyl-1,1-dimethyl-ethylsulfanyl}-acetic acid tert-butyl ester;

1-[4-(Pyridin-4-ylsulfanyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

2(R)-[4-(4-Bromo-phenoxy)benzenesulfonylamino]-3-methyl-3-(pyridin-yl-sulfonyl)-butyric acid, hydroxyamide;

25 trans-2-(2-Biphenyl-4-yl-ethylsulfanyl)-cyclohexanecarboxylic acid
hydroxyamide;

N-[1S-(1H-imidazol-2-yl)-3-methyl-butyl]-3R-[3-(4-pyridin-4-yl-phenyl)-pyrrol-1-yl]-succinamic acid formate;

N-Methyl-3-[3-(4-pyridin-4-yl-phenyl)-pyrrol-1-yl]-succinamic acid;

30 N(4)-(2,2-Dimethyl-1S-hydroxymethyl-propyl)-N(1)-hydroxy-3R-[3-(4-pyridin-4-yl-phenyl)-pyrrol-1-yl]-succindiamide:

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3R-[3-(4-Cyano-phenyl)-pyrrol-1-yl]-N-(2,2-dimethyl-1S-methylcarbamoyl-propyl)-succinamic acid;

2-[4-(4-Fluorophenoxy)-benzenesulfonylamino]-3-methyl-3-(hydroxyethylsulfanyl)-butyric acid;

5 [4-Methoxy-benzenesulfonylamino]-3-methyl-3-(pyridin-2-yl-sulfanyl)-butyric acid;

N-(4,4-Dimethyl-2-oxo-tetrahydro-furan-3S-yl)-3R-[1-(4'-cyanobiphenyl-4-yl)-1H-pyrrol-3-yl]-succinamic acid;

10 2-[4-(4-Fluorophenoxy)-benzenesulfonylamino]-3-methyl-3-(amidoethylsulfanyl)-butyric acid;

[4-Methoxy-benzenesulfonylamino]-3-methyl-3-(pyridin-2-ylsulfanyl)-butyric acid;

2-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-3,3-dimethyl-5-phenyl-pent-4-enoic acid;

15 5-[4-(4-Fluoro-phenoxy)-benzenesulfonyl]-4,5,6,7-tetrahydro-3H-imidazole[4,5,-c]pyridine-6-carboxylic acid hydroxyamide

2(R)-[4-(4-Methylphenoxy)benzenesulfonylamino]-3-methyl-3-(pyridin-yl-sulfonyl)butyric acid;

20 3(S)-4-(4-((Pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid;

1-[4-(Pyridin-4-ylsulfanyl)-piperidine-1-sulfanyl]-piperidine-2-carboxylic acid hydroxyamide;

N-[1-(1H-imidazol-2-yl)-3-methyl-butyl]-3-[1-(4'-cyanobiphenyl-4-yl)-1H-pyrrol-3-yl]-succinamic acid;

25 3R-{3-[(4-Cyano-phenyl)-acetyl]-pyrrol-1-yl}-N-(2,2-dimethyl-1S-methylcarbamoyl-propyl)-succinamic acid;

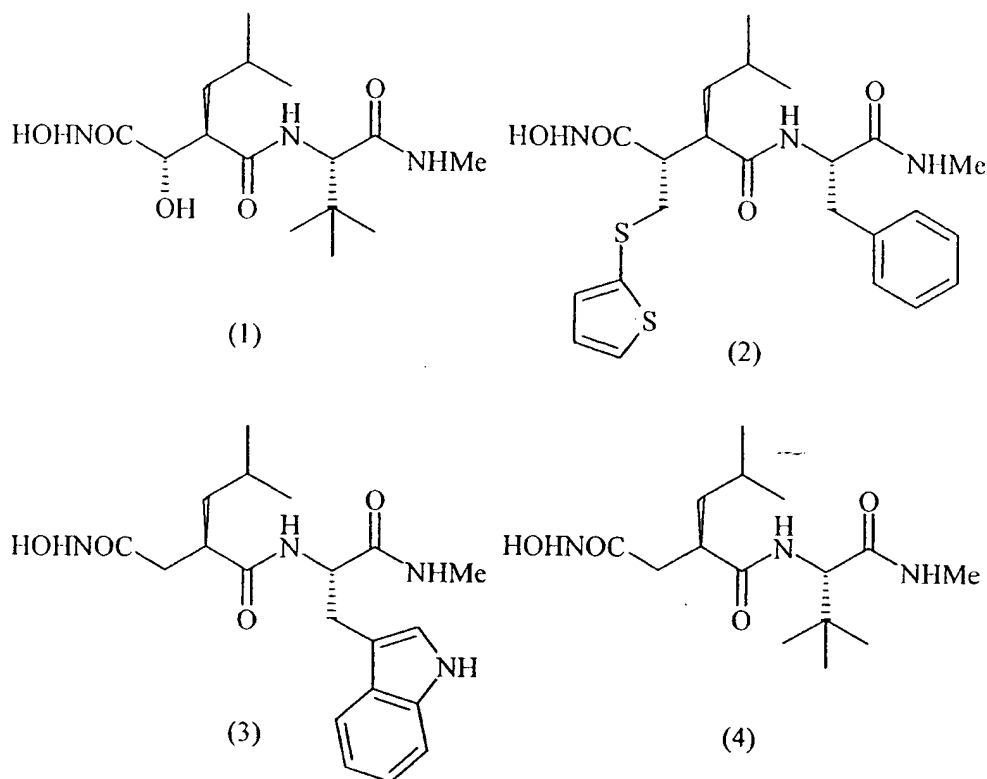
1-[4-(4-Methoxy-phenylsulfamyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxamide;

30 3R-[3-(4-Cyano-phenyl)-pyrrol-1-yl]-N-(2,2-dimethyl-1S-methylcarbamoyl-propyl)-succinamic acid methyl ester;

2(R)-[4-(4-Methylphenoxy)benzenesulfonylamino]-3-methyl-3-(pyridin-yl-sulfonyl)butyric acid, hydroxyamide;

- 3,3-Dimethyl-2R-[4-(pyridin-4-ylsulfanyl)-piperidine-1-sulfonylamino]-butyric acid;
- 3,3-Dimethyl-N-hydroxy-2R-[4-(pyridin-4-ylsulfanyl)-piperidine-1-sulfonylamino]-butyramide;
- 5 2R-[4-(4-Bromophenoxy)-benzenesulfonylamino]-N-hydroxy-3-methyl-3-[(1-methyl-imidazol-2-yl)methylsulfanyl]-butyramide;
- 2R-[4-(4-Bromophenoxy)-benzenesulfonylamino]-3-methyl-3-[(1-methyl-imidazol-2-yl)methylsulfanyl]-butyric acid;
- N-Hydroxy-2-[(4-methylbenzenesulfonyl)amino]acetamide;
- 10 1-[4-(4-Imidazol-1-yl-phenoxy)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;
- 1-[4-(4-Imidazol-1-yl-phenylsulfanyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;
- 2(R)-[4-(4-Chloro-benzoyl)-cyclohexanesulfonyl]-piperidine-1-carboxylic acid hydroxyamide;
- 15 1(R)-[4-(4-Chloro-benzoyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid amide;
- 1(R)-(4-Pyridin-2-yl-piperazine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;
- 20 1(R)-[4-(4-Imidazol-1-yl-phenoxy)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid;
- 1(R)-[4-(4-Imidazol-1-yl-phenoxy)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;
- N-Hydroxy-3,3-dimethyl-2R-[4-(morpholine-4-carbonyl)piperidine-1-sulfonylamino]butyramide;
- 25 N-Hydroxy-3-methyl-3-(5-methyl-isoxazol-3-yl-methylsulfanyl)-2R-[4-(pyridin-4-ylsulfanyl)-piperidine-sulfonylamino]-butyramide;
- 4-(4'-Chloro-biphenyl-4-yl)-2RS-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-butyric acid;
- 30 4-(4'-Chloro-biphenyl-4-yl)-2R-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-butyric acid;

Compounds in Clinical Development



All that is required to practice the present invention is to administer to a mammal suffering from atherosclerosis, an effective amount of a matrix metalloproteinase inhibitor and an ACAT inhibitor. Compounds which can inhibit the actions of matrix metalloproteinase enzymes can be identified utilizing routine in vitro and in vivo assays. Several compounds from within the foregoing classes have been evaluated in such standard assays and determined to be potent matrix metalloproteinase inhibitors. The assays measure the amount by which a test compound reduces the hydrolysis of a thiopeptolide substrate caused by a matrix metalloproteinase enzyme. Such assays are described in detail by Ye, et al., in Biochemistry, Vol. 31, No 45, 1992, (11231-11235), which is incorporated herein by reference.

Thiopeptolide substrates show virtually no decomposition or hydrolysis in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-O Et. A 100 μ L assay mixture will contain 50 mM of 2-morpholinoethane sulfonic acid monohydrate (MES, pH 6.0) 10 mM CaCl_2 , 100 μ M thiopeptolide

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- (a) phenyl or phenoxy each of which is unsubstituted or is substituted with 1 to 5 substituents selected from

phenyl,

an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,

an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;

phenoxy,

hydroxy,

fluorine,

chlorine,

bromine,

nitro,

trifluoromethyl,

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,

-(CH₂)_pNR₃R₄ wherein p is zero or one, and each of

R₃ and R₄ is selected from hydrogen or a straight or

branched alkyl group having 1 to 4 carbon atoms;

- (b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to 3 substituents selected from

phenyl,

an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,

an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;

hydroxy,

phenoxy,

fluorine,

chlorine,

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R₅ and R₆ are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₅ is hydrogen, R₆ can be selected from the groups defined for R₇; and

R₇ is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, COOalkyl wherein alkyl has from 1 to 4 carbon atoms, or -(CH₂)_pNR₃R₄ wherein P, R₃ and R₄ have the meanings defined above.

Also preferred compounds of the instant invention are those of Formula I wherein

X is oxygen, sulfur or (CR'R'')_n;

Y is oxygen, sulfur or (CR'R'')_n, with the proviso that at least one of X or Y is

(CR'R'')_n wherein n is an integer of from 1 to 4 and R' and R'' are each

independently hydrogen, straight or branched alkyl of from 1 to 6 carbons, optionally substituted phenyl, halogen, hydroxy, alkoxy, acyloxy, cycloalkyl, or R' and R'' taken together form a carbonyl or a spirocycloalkyl group of from 3 to 10 carbons;

R is hydrogen;

R₁ is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 10 carbon atoms;

R₂ is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms, phenoxy optionally substituted with the proviso that only if X is (CR'R'')_n can

R₁ be optionally substituted phenoxy and only if Y is (CR'R'')_n can R₂ be optionally substituted phenoxy, and with the further proviso that at least one of R₁ and R₂ is optionally substituted phenyl or phenoxy.

More preferred compounds of the instant invention are those of Formula I wherein

X is oxygen;

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]carbamate-sodium salt,

5 Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

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- 8-(1,4,5-Triphenyl-2H-imidazol-2-yloxy)-octanoic acid;
- 9-Bromo-6,11-dihydro-dibenzo[b,e]oxepine-11-carboxylic acid (2,6-diisopropyl-phenyl)-amide;
- 5 5-((3,5-Di-tert-butyl-4-hydroxy-phenylamino)-{[4-(2,2-dimethyl-propyl)-benzyl]-hexyl-amino}-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione;
- 3-(2,4-Difluoro-phenyl)-1-[4-(2,2-dimethyl-propyl)-benzyl]-1-heptyl-urea;
- 1-Heptyl-1-[4-(3-methyl-butyl)-benzyl]-3-(2,4,6-trifluoro-phenyl)-urea;
- 3-(2,4-Difluoro-phenyl)-1-[5-(4,5-diphenyl-1H-imidazol-2-ylsulfanyl)-pentyl]-1-heptyl-urea;
- 10 1-Butyl-3-{2-[3-(5-ethyl-4-phenyl-imidazol-1-yl)-propoxy]-6-methyl-phenyl}-urea;
- 1-(2-{4-(2,2-Dimethyl-propyl)-phenyl}-ethyl)-4,6-difluoro-phenyl)-3-heptyl-urea;
- Octadeca-9,12-dienoic acid (1-phenyl-ethyl)-amide;
- 15 3-(1H-Indol-3-yl)-2-octadec-9-enoylamino-propionic acid ethyl ester;
- 3-(Dimethyl-nonyl-silanyl)-N-(1-phenyl-2-p-tolyl-ethyl)-propionamide;
- (R)2-Hexyl-decanoic acid (6-methyl-2,4-bis-methylsulfanyl-pyridin-3-yl)-amide;
- N-[2-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-ethyl]-4-fluoro-
- 20 benzenesulfonamide;
- 2-(2-Ethoxy-ethylsulfanyl)-4,5-diphenyl-1H-imidazole;
- 4-Cyano-N-[2-(4-cyano-phenyl)-3-methyl-5,5-bis-trifluoromethyl-4,5-dihydro-3H-imidazol-4-yl]-N-methyl-benzamide;
- 1-{3-[3-(1-Methyl-1H-imidazol-2-yl)-2-phenethyl-2H-chromen-6-yloxy]-propyl}-cyclopentanecarboxylic acid ethyl ester;
- 25 1-[4-(2-Chloro-phenyl)-2-ethyl-thieno[2,3-b]pyridin-5-yl]-3-(2,4-difluoro-phenyl)-urea;
- 1-(2-Cyclohexyl-[1,3]dithiolan-2-ylmethyl)-3-(2,6-diisopropyl-phenyl)-urea;
- 30 1-Cycloheptyl-1-(2,3-dihydro-benzo[1,4]dioxin-5-ylmethyl)-3-(2,4,6-trimethyl-phenyl)-urea;
- 1-{2-[4-(1,2-Dimethoxy-ethoxy)-phenyl]-ethyl}-3-(2,4-dimethoxy-phenyl)-1-heptyl-urea;

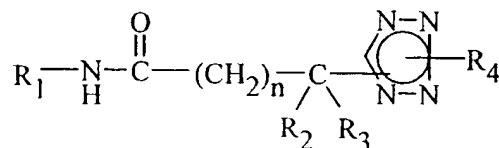
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- 1-(2-{2-[4-(2,2-Dimethyl-propyl)-phenyl]-ethyl}-4,6-difluoro-phenyl)-
3-heptyl-urea;
- (4S-trans)6-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-4-hydroxy-
4-methyl-tetrahydro-pyran-2-one;
- 5 2-(3-[1,3]Dioxan-2-yl-propylsulfanyl)-4,5-diphenyl-1H-imidazole;
Hydroxy-phenyl-acetic acid 3,3,5-trimethyl-cyclohexyl ester;
Acetic acid 1-(11-hydroxy-4-methoxy-9-methyl-5-oxo-5H,7H-6,12-dioxo-
dibenzo[a,d]cycloocten-3-yl)-3-methyl-butyl ester;
- 10 10-Hydroxy-2,4a,6a,6b,9,10,12a-heptamethyl-4-octadecanoyloxy-
1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10, 11,12,12a,12b,13,14b-eicosahydro-picene-
2-carboxylic acid;
- 3-[(2,2,5,5-Tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-propionic acid
2-[3-(2,2-dimethyl-propyl)-3-nonyl-ureido]-cyclohexyl ester;
- 1-(2,6-Diisopropyl-phenyl)-3-(2-p-tolyl-heptyl)-urea;
- 15 1-[4-(2-Chloro-phenyl)-6,8-dimethyl-quinolin-3-yl]-3-(2,4-difluoro-
phenyl)-urea;
- 1-[4-(2-Chloro-phenyl)-1,6,7-trimethyl-2-oxo-1,2-dihydro-quinolin-3-yl]-
3-(2,4-difluoro-phenyl)-urea;
- 1-[4-(2-Chloro-phenyl)-6,7-dimethyl-2-oxo-2H-chromen-3-yl]-
20 3-(2,4-difluoro-phenyl)-urea;
- (S)1-[6-Bromo-5-(2-chloro-phenyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-
benzo[e][1,4]diazepin-7-yl]-3-(2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-urea;
- 3-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-methyl-piperidine;
- 2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-4,5-diphenyl-1H-imidazole;
- 25 2,2-Dimethyl-5-[3-(1-methyl-1H-imidazol-2-yl)-2-propyl-chroman-
6-yloxy]-pentanoic acid ethyl ester;
- N-(4-Hexadecylamino-benzoyl)-4-methyl-benzenesulfonamide;
- 2-(4-Chloro-phenyl)-6-cyclohexyl-4-(2-oxo-2-phenyl-ethyl)-6,7-dihydro-
4H-1,4,6,8a-tetraaza-s-indacene-5,8-dione;
- 30 [2-(3-tert-Butyl-4-hydroxy-naphthalen-1-yl)-1-(diethoxy-phosphoryl)-
vinyl]-phosphonic acid diethyl ester;

METHODS

The direct antiatherosclerotic potential of ACAT and MMP inhibitors is evaluated in a model of atherosclerotic lesion regression. Male New Zealand White rabbits (Kuiper Farms, Gary, Indiana) weighing 1.2 to 1.5 kg are meal-fed a chow diet (Purina 5321) supplemented with 0.5% cholesterol (C), 3% peanut (PNO) oil, and 3% coconut (CNO) oil diet for a total of 9 weeks followed by a 0% C, 3% PNO, and 3% CNO diet (chow/fat diet) for 6 weeks prior to an 8-week administration of the ACAT inhibitor, for example, sulfamic acid[[2,4,6-tris-(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester, the HMG-CoA reductase inhibitor, for example, simvastatin, either alone or together. The dietary regimen consists of feeding 30 g for the first week, 40 g for 2 weeks, 50 g for 2 weeks, 60 g for 4 weeks, 70 g for the next 6 weeks, and 80 g for the final 8 weeks. After 1 week of diet initiation, a chronic endothelial injury is induced in the abdominal aorta and femoral artery by surgically inserting a sterile, indwelling, 18-cm nylon monofilament with a diameter of 200 μ M into the lumen of the right femoral artery. After the initial 15-week lesion induction phase, which consists of both a hypercholesterolemic and plasma cholesterol normalization stage, the animals are randomized on the basis of their 24-hour postmeal plasma total cholesterol values into groups which are not statistically different. A group of animals, termed the time zero control (n = 16), is necropsied prior to drug administration while a second group, termed the progression control (n = 16), is maintained on the chow/fat diet for the remaining 8 weeks of the study. Additional groups of animals are administered either ACAT inhibitors, MMP inhibitors, or coadministered both compounds.

Other ACAT inhibitors useful in the practice of the instant invention are those of Formula 1 below



wherein n is zero, one or two;

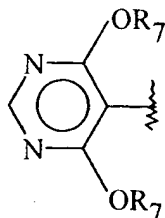
wherein R₁ is selected from

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-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,

$-(CH_2)_mNR_5R_6$ wherein m, R_5 , and R_6 have the meanings defined above;

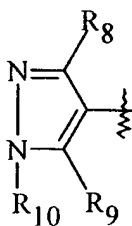
(c) the group



5

wherein R_7 is a lower alkyl group having from 1 to 3 carbon atoms and is straight or branched;

(d) the group



10

wherein R_8 and R_9 are straight or branched alkyl having from 1 to

4 carbon atoms or phenyl, and R_{10} is a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing one double bond or two nonadjacent double bonds; phenyl; phenyl substituted with from one to three substituents selected from straight or branched alkyl having 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 3 carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, -COOH, -COOalkyl wherein alkyl

15

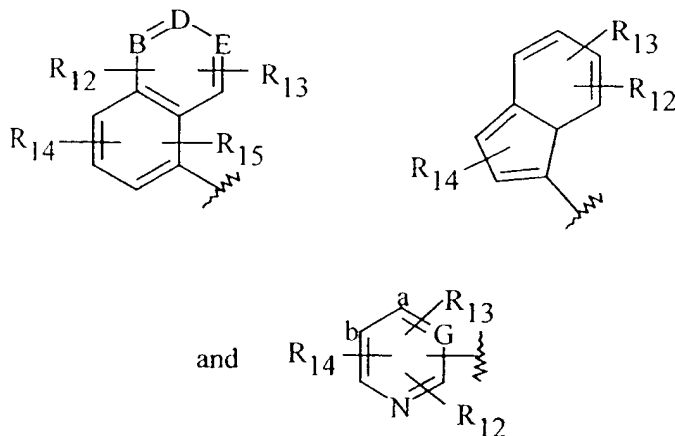
20

has from 1 to 4 carbon atoms and is straight or branched or $-(CH_2)_mNR_5R_6$ wherein m, R_5 , and R_6 are as defined above; or a heterocyclic group selected from 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-pyrazinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, or 3- or 4-pyridazinyl and the N-oxides thereof;

(e) the group

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(k) is selected from the group



wherein R_{12} , R_{13} , R_{14} , and R_{15} are each independently hydrogen, halo, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms, and alkylthio group of 1 to 3 carbon atoms, cycloalkylthio of five to seven carbon atoms, phenylalkylthio in which alkyl is 1 to 4 carbon atoms, substituted phenylthio, heteroarylthio, or heteroaryloxy; and B, D, E, and G are nitrogen or carbon where one or more of B, D, and E is nitrogen; with the proviso that when G = nitrogen the group is attached to the nitrogen atom of Formula I at the 4- or 5-position of the pyrimidine ring (a and b);

wherein R_2 and R_3 are the same or different and are selected from:

- (a) hydrogen, halo or one of R_2 or R_3 is hydroxy;
- (b) a straight or branched alkyl group having from 1 to 12 carbon atoms, or a cycloalkyl group having from 3 to 8 carbon atoms;
- (c) a phenyl or phenylalkyl group where alkyl is from 1 to 4 carbon atoms and which the phenyl ring unsubstituted or substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, alkylthio, straight or branched having 1 to 4 carbon atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, nitro, phenyl, or $(CH_2)_mNR_5R_6$ wherein m, R_5 , and R_6 have the meanings defined above;
- (d) a straight or branched alkenyl group having from 2 to 6 carbon atoms; or

- (±)-N-[2,6-bis(1-Methylethyl)phenyl]-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide;
- (±)-N-(2,4-Difluorophenyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide;
- 5 (±)-2-Octyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;
- (±)-2-Hexadecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;
- 10 (±)-N-(4,6-Dimethoxy-5-pyrimidinyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide;
- (±)-N-(5,7-Dimethyl-1,8-naphthyridine-2-yl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide;
- (±)-2-Dodecyl-α-phenyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide;
- 15 (±)-N-Cyclopropyl-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide;
- (±)-2-Dodecyl-α-phenyl-N-2-pyridinyl-2H-tetrazole-5-acetamide;
- (±)-2-Dodecyl-N-(3-methyl-2-pyridinyl)-α-phenyl-2H-tetrazole-5-acetamide;
- (±)-2-Dodecyl-N-(3-methyl-2-pyridinyl)-2-phenyl-2H-tetrazole-5-acetamide, N-oxide;
- 20 (±)-N-(1,1-Dimethylethyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide;
- (±)-2-Dodecyl-α-(2-pyridyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;
- (±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α-2-pyridinyl-2H-tetrazole-5-acetamide;
- 25 2-Dodecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;
- 2-Dodecyl-α,α'-(2-propenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;
- 30 1-(2-Dodecyl-2H-tetrazol-5-yl)-N-(2,4,6-trimethoxyphenyl)-cyclopentanecarboxamide;

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- N-[2,6-bis(1-Methylethyl)phenyl]-5-decyl-2H-tetrazole-2-acetamide;
 N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl-2H-tetrazole-2-acetamide;
 (±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl-α-phenyl-2H-tetrazole-
 2-acetamide;
 5 (±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl-α-pentyl-2H-tetrazole-
 2-acetamide;
 (±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-(dodecylthio)-α-phenyl-2H-
 tetrazole-2-acetamide;
 (±)-5-Decyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
 10 2-acetamide;
 5-Dodecyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-2-acetamide;
 (±)-5-Dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
 2-acetamide;
 (±)-5-Dodecyl-α-pentyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
 15 2-acetamide;
 (±)-N-(2,4-Difluorophenyl)-5-dodecyl-α-phenyl-2H-tetrazole-2-acetamide;
 5-Dodecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
 2-acetamide;
 (±)-5-(Dodecylthio)-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
 20 2-acetamide; or
 (±)-5-(Dodecylsulfinyl)-α-phenyl-N-(2,4,6)-trimethoxyphenyl)-2H-
 tetrazole-2-acetamide.

The compounds to be employed in the present invention can be prepared
 and administered in a wide variety of oral and parenteral dosage forms for treating
 25 and preventing atherosclerosis. The compounds can be administered by injection,
 that is, intravenously, intramuscularly, intracutaneously, subcutaneously,
 intraduodenally, or intraperitoneally. Also, the compounds can be administered by
 inhalation, for example, intranasally. Additionally, the compounds can be
 administered transdermally. It will be obvious to those skilled in the art that the
 30 following dosage forms may comprise as the active component, either a
 compound as a free base, acid, or a corresponding pharmaceutically acceptable

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

5 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration.
10 Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such
15 form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the
20 appropriate number of any of these in packaged form.

The quantity of active component in a unit-dose preparation may be varied or adjusted from 1 to 1000 mg, preferably 10 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

25 The compounds utilized in the pharmaceutical method of this invention are administered at a dose that is effective to inhibit the hydrolytic activity of one or more matrix metalloproteinase enzymes. Such effective amounts are thus those which prevent or treat CHF and ventricular dilatation. The compounds can also be used prophylactically at the same dose levels. The initial dosage of about 1 mg to
30 about 100 mg per kilogram daily will be effective to prevent and treat heart failure. A daily dose range of about 5 to about 75 mg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed.

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Preparation for Oral Solution

Ingredient	Amount
(R)-2-(4'-Cyanobiphenyl-4-sulfonylamino)-3-phenyl-propionic acid sodium salt	400 mg
ACAT Compound	
Sorbitol solution (70% N.F.)	40 mL
Sodium benzoate	20 mg
Saccharin	5 mg
Red dye	10 mg
Cherry flavor	20 mg
Distilled water q.s.	100 mL

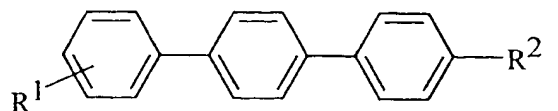
5 The sorbitol solution is added to 40 mL of distilled water, and the biphenylsulfonamide is dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 4 mg of invention compound.

Parenteral Solution

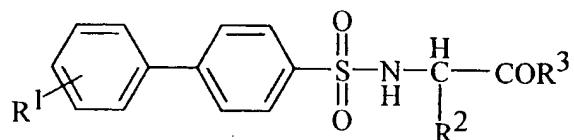
10 In a solution of 700 mL of propylene glycol and 200 mL of water for injection is suspended 20 g of (S)-2-(4'-amino-biphenyl-4-sulfonylamino)-3-(3-ethoxyphenyl)-propionic acid. After suspension is complete, the pH is adjusted to 6.5 with 1N sodium hydroxide, and the volume is made up to 1000 mL with water for injection. The formulation is sterilized, filled into 5.0 mL ampoules each containing 2.0 mL, and sealed under nitrogen.

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5. A method according to Claim 3 employing a compound of the formula



6. A method according to Claim 4 employing a compound of the formula



5 wherein:

R¹ is C₁-C₆ alkyl, halo, nitro, NR⁴R⁵, cyano, OR⁴, and C(O)OR⁴;

R² is C₁-C₆ alkyl, optionally substituted by phenyl, substituted phenyl,

10 NH
|
NR⁴R⁵, OR⁶, carboxy, carboxamido, H₂N-C-NH-, thio,
methylthio, indole, imidazole, phthalimido, phenyl, and substituted
phenyl;

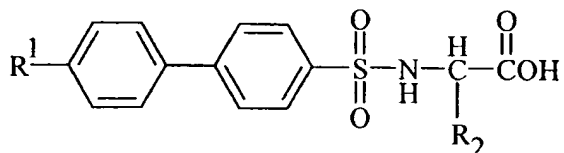
R³ is OH, OC₁-C₆ alkyl, or NHOH;

R⁴ is hydrogen, C₁-C₆ alkyl, or C₁-C₆ alkanoyl;

15 R⁵ is hydrogen or C₁-C₆ alkyl; and

R⁶ is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkanoyl, phenyl, or substituted
phenyl.

7. A method according to Claim 5 employing a compound of the formula



- 20 8. A method according to Claim 6 employing 2-(4'-bromobiphenyl-
4-sulfonylamino)-3-methyl-butyric acid.

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-C-R⁶ wherein R⁶ is as defined above,-CH₂-OR⁶ wherein R⁶ is as defined above,

5 -CH₂-N-R⁶ wherein R⁶ and R^{6a} are the same or different

and are as defined above for R⁶,

10 -C-N-R⁶ wherein R⁶ and R^{6a} are the same or different and

are as defined above for R⁶,

15 -S-R⁶ wherein R⁶ is as defined above,



20 cycloalkyl, or

heteroaryl, with the proviso that R and R¹ are not both hydrogen;R² is -OR⁶ wherein R⁶ is as defined above, or-N-R⁶ wherein R⁶ and R^{6a} are the same or different and are

25 |

as defined above for R⁶;R³, R^{3a}, R⁴, and R^{4a} are the same or different and are hydrogen,

fluorine,

alkyl,

30 -(CH₂)_n-aryl wherein n is an integer from 1 to 6,

-(CH₂)_n-heteroaryl wherein n is as defined above,-(CH₂)_n-cycloalkyl wherein n is as defined above,

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wherein R^6 is as defined above,



wherein R^6 is as defined above, or



wherein R^6 and R^{6a} are the same or different

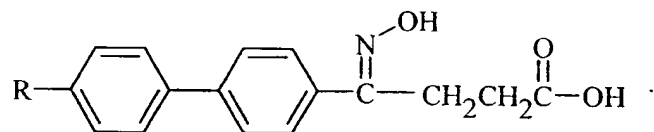
and are as defined above for R^6 , and

n is as defined above;

R^5 is OH or SH; with the proviso that R^3 , R^{3a} , R^4 , and

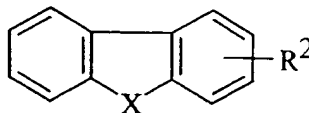
R^{4a} are hydrogen or at least one of R^3 , R^{3a} , R^4 , or R^{4a} is fluorine; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

10. A method according to Claim 8 employing a compound of the formula



11. A method according to Claim 9 employing 4-(4'-chlorobiphenyl-4-yl)-4-hydroxyimino-butyric acid.

12. A method according to Claim 1 employing a compound of the formula



wherein

X is oxygen or $-\text{C}-\text{CH}_2-$

R² is hydrogen or C₁-C₆ alkyl, optionally substituted by the following groups: phenyl, substituted phenyl, phenoxy, substituted phenoxy,

5 NR⁴R⁵, OR⁶, carboxy, carboxamido, H₂N-C(=O)-HN-, thio, methylthio, indole, imidazole, and phthalimido;

R³ is OH, O, C₁-C₆ alkyl, or NHOH;

R⁴ is hydrogen, C₁-C₆ alkyl, or C₁-C₆ alkanoyl;

R⁵ is hydrogen or C₁-C₆ alkyl; and

10 R⁶ is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkanoyl, phenyl, or substituted phenyl, and pharmaceutically acceptable salts and solvates thereof.

17. A method according to Claim 1 wherein the compound employed is selected from

15 (S)-2-(4'-Bromo-biphenyl-4-sulfonylamino)--3-methyl-butyric acid;

(S)-2-(4'-Chloro-biphenyl-4-sulfonylamino)-3-methyl-butyric acid;
(S)-3-Methyl-2-(4'-nitro-biphenyl-4-sulfonylamino)-butyric acid;
(S)-2-(4'-Amino-biphenyl-4-sulfonylamino)-3-methyl-butyric acid;
(S)-2-(4'-Cyano-biphenyl-4-sulfonylamino)-3-methyl-butyric acid;
20 (S)-2-(3',4'-Dibromo-biphenyl-4-sulfonylamino)-3-methyl-butyric
acid, sodium salt;

(S)-2-(3'-Bromo-biphenyl-4-sulfonylamino)-3-methyl-butyrlic acid;
(S)-2-(4'-Bromo-2'-fluoro-biphenyl-4-sulfonylamino)-3-methyl-butyrlic acid,

25 (R)-2-(4'-Bromo-biphenyl-4-sulfonylamino)-3-methyl-butyrlic acid;
(S)-2-(4'-Bromo-biphenyl-4-sulfonylamino)-propionic acid;
(S)-2-(4'-Bromo-biphenyl-4-sulfonylamino)-4-methyl-pentanoic
acid;

30 (S)-2-(4'-Methoxy-biphenyl-4-sulfonylamino)-3-methyl-butyric acid;

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R is hydrogen, a straight or branched alkyl of from 1 to 8 carbon atoms or benzyl;

R₁ and R₂ are each independently selected from

(a) phenyl or phenoxy each of which is unsubstituted or is substituted
5 with 1 to 5 substituents selected from

phenyl,

an alkyl group having from 1 to 6 carbon atoms and which
is straight or branched,

an alkoxy group having from 1 to 6 carbon atoms and
10 which is straight or branched;

phenoxy,

hydroxy,

fluorine,

chlorine,

15 bromine,

nitro,

trifluoromethyl,

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and
20 is straight or branched,

-(CH₂)_pNR₃R₄ wherein p is zero or one, and each of

R₃ and R₄ is selected from hydrogen or a straight or
branched alkyl group having 1 to 4 carbon atoms;

(b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to
25 3 substituents selected from

phenyl,

an alkyl group having from 1 to 6 carbon atoms and which
is straight or branched,

an alkoxy group having from 1 to 6 carbon atoms and
30 which is straight or branched;

hydroxy,

phenoxy,

25. A compound of Claim 14 wherein R₁ is phenyl disubstituted in the 2,6-positions and R₂ is phenyl trisubstituted in the 2,4,6-positions.
26. A compound of Claim 14 wherein R₁ is 2,6-bis(1-methylethyl)phenyl and R₂ is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl.
- 5 27. A compound of Claim 14 wherein R₁ is phenyl or isophenyl disubstituted in the 2,6-positions, wherein R₂ is phenyl or is phenyl disubstituted in the 2,6-positions, wherein each of R₁ and R₂ is phenyl, wherein each phenyl is disubstituted in the 2,6-position, wherein R₁ is phenyl disubstituted in the 2,6-positions and R₂ is phenyl trisubstituted in the 2,4,6-positions,
10 wherein R₁ is 2,6-bis(1-methylethyl)phenyl and R₂ is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl, wherein one of R₁ and R₂ is the group



- wherein t is zero or 1 to 4; w is zero or 1 to 4 with the proviso that the sum of t and w is not greater than 5; R₅ and R₆ are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₅ is hydrogen, R₆ can be selected from the groups defined for R₇; and R₇ is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy,
20 hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, COOalkyl wherein alkyl has from 1 to 4 carbon atoms, or -(CH₂)_pNR₃R₄ wherein P, R₃ and R₄ have the meanings defined above.
- 25

28. A compound according to Claim 14 wherein

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Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

5 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis[1-methylethyl)phenyl ester,

10 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

15 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]benzeneacetamide,

2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]benzeneacetamide-sodium salt,

20 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]carbamate-sodium salt,

Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

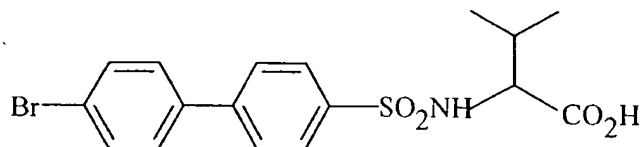
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

32. A method according to Claim 1 wherein the MMP inhibitor is selected from

25



and

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- 8-(1,4,5-Triphenyl-2H-imidazol-2-yloxy)-octanoic acid;
9-Bromo-6,11-dihydro-dibenzo[b,e]oxepine-11-carboxylic acid
(2,6-diisopropyl-phenyl)-amide;
5 5-((3,5-Di-tert-butyl-4-hydroxy-phenylamino)-{[4-(2,2-dimethyl-propyl)-benzyl]-hexyl-amino}-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione;
3-(2,4-Difluoro-phenyl)-1-[4-(2,2-dimethyl-propyl)-benzyl]-1-heptyl-urea;
1-Heptyl-1-[4-(3-methyl-butyl)-benzyl]-3-(2,4,6-trifluoro-phenyl)-
10 urea;
3-(2,4-Difluoro-phenyl)-1-[5-(4,5-diphenyl-1H-imidazol-2-ylsulfanyl)-pentyl]-1-heptyl-urea;
1-Butyl-3-{2-[3-(5-ethyl-4-phenyl-imidazol-1-yl)-propoxy]-6-methyl-phenyl}-urea;
15 1-(2-{2-[4-(2,2-Dimethyl-propyl)-phenyl]-ethyl}-4,6-difluoro-phenyl)-3-heptyl-urea;
Octadeca-9,12-dienoic acid (1-phenyl-ethyl)-amide;
3-(1H-Indol-3-yl)-2-octadec-9-enoylamino-propionic acid ethyl
ester;
20 3-(Dimethyl-nonyl-silanyl)-N-(1-phenyl-2-p-tolyl-ethyl)-propionamide;
(R)2-Hexyl-decanoic acid (6-methyl-2,4-bis-methylsulfanyl-pyridin-3-yl)-amide;
N-[2-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-ethyl]-4-fluoro-
25 benzenesulfonamide;
2-(2-Ethoxy-ethylsulfanyl)-4,5-diphenyl-1H-imidazole;
4-Cyano-N-[2-(4-cyano-phenyl)-3-methyl-5,5-bis-trifluoromethyl-4,5-dihydro-3H-imidazol-4-yl]-N-methyl-benzamide;
1-{3-[3-(1-Methyl-1H-imidazol-2-yl)-2-phenethyl-2H-chromen-
30 6-yloxy]-propyl}-cyclopentanecarboxylic acid ethyl ester;
1-[4-(2-Chloro-phenyl)-2-ethyl-thieno[2,3-b]pyridin-5-yl]-3-(2,4-difluoro-phenyl)-urea;

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(trans)1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propyl)-azetidin-2-one;

1-Butyl-3-{2-dimethylamino-6-[3-(4-phenyl-imidazol-1-yl)-propoxy]-phenyl}-urea;

5 1-{2-Dimethylamino-6-[3-(4-phenyl-imidazol-1-yl)-propoxy]-phenyl}-3-pentyl-urea;

1-{2-Dimethylamino-6-[3-(5-methyl-4-phenyl-imidazol-1-yl)-propoxy]-phenyl}-3-pentyl-urea;

10 1-(2-{2-[4-(2,2-Dimethyl-propyl)-phenyl]-ethyl}-4,6-difluorophenyl)-3-heptyl-urea;

(4S-trans)6-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-4-hydroxy-4-methyl-tetrahydro-pyran-2-one;

2-(3-[1,3]Dioxan-2-yl-propylsulfanyl)-4,5-diphenyl-1H-imidazole;

Hydroxy-phenyl-acetic acid 3,3,5-trimethyl-cyclohexyl ester;

15 Acetic acid 1-(11-hydroxy-4-methoxy-9-methyl-5-oxo-5H,7H-6,12-dioxo-dibenzo[a,d]-cycloocten-3-yl)-3-methyl-butyl ester;

10-Hydroxy-2,4a,6a,6b,9,10,12a-heptamethyl-4-octadecanoyloxy-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-eicosahydro-picene-2-carboxylic acid;

20 3-[(2,2,5,5-Tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-propionic acid 2-[3-(2,2-dimethyl-propyl)-3-nonyl-ureido]-cyclohexyl ester;

1-(2,6-Diisopropyl-phenyl)-3-(2-p-tolyl-heptyl)-urea;

25 1-[4-(2-Chloro-phenyl)-6,8-dimethyl-quinolin-3-yl]-3-(2,4-difluoro-phenyl)-urea;

1-[4-(2-Chloro-phenyl)-1,6,7-trimethyl-2-oxo-1,2-dihydro-quinolin-3-yl]-3-(2,4-difluoro-phenyl)-urea;

1-[4-(2-Chloro-phenyl)-6,7-dimethyl-2-oxo-2H-chromen-3-yl]-3-(2,4-difluoro-phenyl)-urea;

30 (S)1-[6-Bromo-5-(2-chloro-phenyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-7-yl]-3-(2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-urea;

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4-[2-(2-Carboxymethyl-4-methyl-valeryl-amino)-3,3-dimethyl-butyl-amino]-benzoic acid methyl ester;

4-[2-(2-Hydroxaminocarbonylmethyl-5-methyl-valeryl-amino)-3,3-dimethyl-butyl-amino]-benzoic acid methyl ester;

5 4-[2-(2-Carboxymethyl-4-phenyl-butyl-amino)-2-cyclohexylpropionyl-amino]benzoic acid methyl ester;

4-[2-(2-Carboxymethyl-4-methyl-valeryl-amino)-4-methyl-valeryl-amino]-benzoic acid methyl ester;

10 4-[2-(2-Carboxymethyl-5-phenyl-valeryl-amino)-3,3-dimethyl-butyl-amino]-benzoic acid methyl ester;

4-[2-(2-Carboxymethyl-4-methyl-pentanoyl-amino)-3-(1H-indol-3-yl)-propionyl-amino]-benzoic acid methyl ester;

5-Methyl-3-(9-oxo-1,8-diaza-tricyclo[10.6.1.0 13,18]nonadeca-12(19),13,15,17-tetraen-10-ylcarbamoyl)-hexanoic acid;

15 4-[2-(2-Hydroxaminocarbonylmethyl-4-phenyl-butyl-amino)-3,3-methyl-butyl-amino]-benzoic acid methyl ester;

4-[2-(2-Hydroxaminocarbonylmethyl-4-phenyl-butyl-amino)-2-cyclohexylpropionyl-amino]-benzoic acid methyl ester benzoic acid methyl ester;

20 4-[2-(2-Hydroxaminocarbonylmethyl-4-methyl-valeryl-amino)-4-methyl-valeryl-amino]-benzoic acid methyl ester;

4-[2-(2-Hydroxaminocarbonylmethyl-4-phenyl-butyl-amino)-3-cyclohexylpropionyl-amino]benzoic acid methyl ester;

25 4-[2-(2-Methoxyaminocarbonylmethyl-4-phenyl-butyl-amino)-3-cyclohexylpropionyl-amino]benzoic acid methyl ester;

4-[2-(2-Hydroxaminocarbonylmethyl-5-phenyl-valeryl-amino)-3,3-dimethyl-butyl-amino]-benzoic acid methyl ester;

5-Methyl-3-(9-oxo-1,8-diaza-tricyclo[10.6.1.0,13,18]nonadeca-12(19),13,15,17-tetraen-10-ylcarbamoyl)-1-hexylhydroxamic acid;

30 4-[2-(2-Hydroxaminocarbonylmethyl-4-methyl-pentanoyl-amino)-3-(1H-indol-3-yl)-propionyl-amino]-benzoic acid methyl ester;

3-[2-(4-Methoxy-benzylsulfanyl)-2-methyl-1-phenylcarbamoyl-propylcarbamoyl]-5-methyl-hexanoic acid;

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- 4-[2-(2-Carboxymethyl-5-(N'-methylureido)valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 4-[2-(2-Carboxymethyl-5-(trifluoroacetamido)valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 5 4-[2-(2-Carboxymethyl-2-phenylacetyl-amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 4-[2-(2-Hydroxaminocarbonylmethyl-2-phenylacetyl-amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 10 4-[2-(2-Carboxymethyl-4-methyl-pentanoylamino)-2-cyclohexyl-acetyl-amino]-benzoic acid methyl ester;
- 2-[3-(3-Amino-phenyl)-propyl]-benzohydroxamic acid;
- cis-4-Benzyl-oxy-pyrrolidine-2-carboxylic acid;
- 4-[2-(2-Carboxymethyl-5-(3-amino-4-(trifluoromethyl)phenyl)-valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 15 4-[2-(2-Carboxymethyl-5-(methanesulfamido)valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- N-Cbz-L-Tyrosine;
- N-Boc-L-Tryptophan;
- 4-[2-(Carboxy-2-o-tolyl-propionyl-amino-4-methyl-pentanoylamino)-benzoic acid methyl ester;
- 20 4-[2-(Carboxymethyl-hepanoylamino)-4-methyl-pentanoylamino]-benzoic acid methyl ester;
- 4-[2-(2-Carboxymethyl-5-(4-n-butylphenyl)-valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 25 4-[2-(2-Carboxymethyl-5-(4-n-butylphenyl)-4-pentenoyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 4-[2-(2-Carboxymethyl-2-(2-thienyl)acetyl-amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 4-[2-(2-Carboxymethyl-4-(3-aminophenyl)-butyryl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 30 4-[2-(2-Carboxymethyl-5-(biphen-4-yl)-valeroyl)amino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;

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- 3-[1-(5,6-Dichloro-1H-benzimidazol-2-yl)-3-methyl-butylcarbamoyl]-5-methyl-hexanoic acid;
- 6-Biphenyl-4-yl-3-[1-(5,6-dichloro-1H-benzimidazol-2-yl)-3-methyl-butylcarbamoyl]-5-methyl-hexanoic acid;
- 5 2-Carboxymethyl-heptanoyl-2-(N-methylcarboxamide)piperidine;
- 4-[2-(2-(2-Phenylcyclopropyl)succinylamino)-4-methyl-valeroyl]aminobenzoic acid methyl ester;
- 2-Carboxymethyl-heptanoyl-3-(N-methylcarboxamide)-hexahydropyridazine;
- 10 6-Biphenyl-4-yl-3-[1-[3-(3-hydroxy-ethyl)-phenylcarbamoyl]-2,2-dimethyl-propylcarbamoyl]-hexanoic acid;
- 2R-(3-(4-Biphenyl)propyl)-N-(2R-hydroxy-3-(2-hydroxyphenyl)-5-methyl-3S-hexyl)succinamide;
- 6-Biphenyl-4-yl-3-[1-[3-(2-aminoethyl)-phenylcarbamoyl]-2,2-
- 15 dimethyl-propylcarbamoyl]-hexanoic acid;
- 2R-(3-(4-Biphenyl)propyl)-N-(diphenylmethyl)succinamide;
- 2R-(3-(4-Biphenyl)propyl)-N-(phenylmethyl)succinamide;
- 2-(2-Oxo-imidazolidin-4-ylmethyl)-5-phenyl-pentanoic acid;
- 2-(3-Biphenyl-4-yl-propyl)-N¹-[1-(5,6-dichloro-1H-
- 20 benzoimidazol-2-yl)-3-methyl-butyl]-N⁴-hydroxy-succinamide hexanoic acid;
- 6-Biphenyl-4-yl-[2,2-dimethyl-1-(pyridin-4-ylcarbamoyl)-propylcarbamoyl]-hexanoic acid, N-hydroxyamide;
- 2R-(3-(4-Biphenyl)propyl)-N-((1-hydroxy-1-
- 25 methylethyl)phenylmethyl)succinamide;
- 6-Biphenyl-4-yl-3-[1-phenylcarbamoyl-2-(4-cyano-benzylsulfanyl)-2-methyl-propylcarbamoyl]-hexanoic acid;
- 4-{2-[2-Carboxymethyl-5-(4'-hydroxy-biphenyl-4-yl)-pentanoylamino]-4-methyl-pentanoylamino}-benzoic acid methyl ester;
- 30 1-(N-Methyl-N-phenethylthiocarbonyl)-pyrrolidine-2-carboxylic acid;

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6-Biphenyl-4-yl-3-[cyclohexyl-(4-(2-dimethylamino-ethylsulfamoyl)-phenylcarbamoyl)-methylcarbamoyl]-hexanoic acid, trifluoroacetate salt;

5 4-(2-{2-Carboxymethyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-pentanoylamino}-4-methyl-pentanoylamino)-benzoic acid methyl ester;

4-[2-(2-Carboxymethyl-5-(4-(2-hydroxy-ethyl)-phenyl)-pentanoylamino)-4-methyl-pentanoylamino]-benzoic acid methyl ester;

10 4-(2-{[5-Hydroxyamino-3-(3-phenyl-propyl)-3,4-dihydro-2-H-pyrrole-3-carbonyl]-amino}-4-methyl-pentanoylamino)benzoic acid methyl ester;

5-Hydroxyamino-3-(3-phenyl-propyl)-3,4-dihydro-2-H-pyrrole-3-carboxylic acid(2-cyclohexyl-1-methylcarbamoyl-ethyl)amide;

6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(4-(3-morpholin-4-yl-sulfamoyl)-phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;

15 6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(4-methylsulfanyl-phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;

6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(4-methylsulfonyl-phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;

20 4-[2-(5-Biphenyl-4-yl-2-carboxymethyl-pentanoylamino)-pent-4-enoylamino]-benzoic acid methyl ester;

6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(4-methylsulfinyl-phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;

4-(2-{[5-Hydroxyamino-3-(3-pentyl)-3,4-dihydro-2-H-pyrrole-3-carbonyl]-amino}-4-methyl-pentanoylamino)benzoic acid methyl ester;

25 5-Hydroxyamino-3-(3-pentyl)-3,4-dihydro-2-H-pyrrole-3-carboxylic acid(2-cyclohexyl-1-methylcarbamoyl-ethyl)amide;

6-Biphenyl-4-yl-[2,2-dimethyl-1-(pyridin-4-ylcarbamoyl)-propylcarbamoyl]-hexanoic acid;

30 4-[2-(2-Carboxymethyl-5-(4-cyano-biphenyl-4-yl)-pentanoylamino)-4-methyl-pentanoylamino]-benzoic acid methyl ester;

6-Biphenyl-4-y-3-(R)-(2-hydroxy-1-(S)-phenyl-ethylcarbamoyl)-hexanoic acid;

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- 4-{2-[2-Carboxymethyl-5-(2-fluoro-biphenyl-4-yl)-
pentanoylamino]-4-methyl-pentanoylamino}-benzoic acid methyl ester;
6-Biphenyl-4-yl-3(R)-(1(S)-hydroxymethyl-2,2-dimethyl-
propylcarbamoyl)-hexanoic acid;
- 5 4-{2-[5-Biphen-4-yl-2-(1-carboxy-ethylamino)-pentanoylamino]-
4-methyl-pentanoylamino}-benzoic acid methyl ester;
6-Biphenyl-4-yl-3(R)-(1(S)-hydroxymethyl-2,2-dimethyl-
propylcarbamoyl)-hexanehydroxamic acid;
- 10 6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(4-methylsulfinyl-
phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;
2-(Biphenyl-4-ylsulfonyl)-cyclohex-1-enecarboxylic acid
hydroxyamide;
6-(Biphenyl-4-ylsulfonyl)-cyclohex-1-enecarboxylic acid
hydroxyamide;
- 15 2-Phenethylsulfanyl-cyclohex-1-enecarboxylic acid hydroxyamide;
6-(4'-cyano-biphenyl-4-yl)-3-[2-hydroxy-1-(4-methylsulfinyl-
phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;
- 20 1-{1-[1-(4-Methoxycarbonyl-phenylcarbamoyl)-3-methyl-
butylcarbamoyl]-3-methyl-butylcarbamoyl}-pyrrolidine-2-carboxylic acid;
6-Biphenyl-4-yl-3-[2,2-dimethyl-1-(4S-methylsulfinyl-
phenylcarbamoyl)-propylcarbamoyl]-hexanoic acid;
- 4-[2-(2-Carboxymethyl-5-(4-(2-hydroxy-3,3,3-trifluoropropyl)-
phenyl)-pentanoylamino)-4-methyl-pentanoylamino]-benzoic acid methyl
ester;
- 25 2-Benzylsulfanyl-cyclohexanecarboxylic acid hydroxamide;
1-{1-[1-(4-Methoxycarbonyl-phenylcarbamoyl)-3-methyl-
butylcarbamoyl]-3-methyl-butylcarbamoyl}-pyrrolidine-2-carboxylic acid;
trans-2-Benzylsulfanyl-cyclohexanecarboxylic acid hydroxamide;
- 30 4-[2-(2-Carboxymethyl-5-(4-(2-methylthiazol-4-yl)phenyl)-
valeroyl)amino]-4-methyl-valeroyl]aminobenzoic acid methyl ester;

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trans-2-(4-Phenoxy-benzylsulfanyl)-cyclohexancarboxylic acid
hydroxamide;

2-(4-Indol-1-yl-benzylsulfanyl)-cyclohexancarboxylic acid
hydroxamide;

5 6-Biphenyl-4-yl-3-[2-hydroxy-2-methyl-1-(4S-methylsulfinyl)-
phenylcarbamoyl]-propylcarbamoyl]-hexanoic acid;

6-Biphenyl-4-yl-3-(2,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-
pyran-3-ylcarbamoyl)-hexanoic acid;

10 5-Biphenyl-4-yl-2-[(formyl-hydroxy-amino)-methyl]-pentanoic
acid{1-[4-(2-dimethylamino-ethylsulfamoyl)-phenylcarbamoyl]-3-methyl-
butyl}-amide;

2-(3-Biphenyl-4-yl-propyl)-N⁴-hydroxy-N1-(2,4,5-trihydroxy-6-
hydroxymethyl-tetrahydro-pyran-3-yl)-succinamide;

15 6-Biphenyl-4-yl-3-(2,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-
pyran-3-ylcarbamoyl)-hexanoic acid;

N-[2,2-Dimethyl-1S-(pyridin-4-ylcarbamoyl)-propyl]-3R-
thiophen-3-yl-succinamic acid;

4-[2S-(2R-(3-Biphenyl-4-yl-pyrrol-1-yl)-3-carboxy-
propionylamido)-4-methyl-pentanoylamino]-benzoic acid methyl ester;

20 3-(R)-(2-Benzylloxy-phenyl)-1-(S)-hydroxymethyl-
ethylcarbamoyl)-6-biphenyl-4-yl-hexanoic acid;

6-Biphenyl-4-yl-3-(R)-(2-hydroxy-1-(S)-(4-hydroxy-benzyl)-
ethylcarbamoyl)-hexanoic acid;

6-Biphenyl-4-yl-3-(1-hydroxyimino-ethyl)-hexanoic acid;

25 N-[2-(3-(4-biphenyl)propyl)-5,5-difluoro-4-oxopentanoyl]-L-t-
leucine, N'-4-(methylthio)phenyl amide;

6-Biphenyl-4-yl-3-(R)-(2-hydroxy-1-(S)-(4-hydroxy-benzyl)-
ethylcarbamoyl)-hexanehydroxamic acid;

30 4-{2-[2-carboxymethyl-5-(4'-sulfamoyl-biphenyl-4-yl)-
pentanoylamino]-4-methyl-pentanoylamino}-benzoic acid methyl ester;

2-(2-Biphenyl-4-yl-ethylsulfanyl)-cyclohexane carboxylic acid
hydroxyamide;

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1-[4-Bromo-phenoxy)-benzenesulfonyl)-piperidine-2-carboxylic
acidhydroxyamide;

N-(1-Benzyl-2-methoxy-ethyl)-3-(3-biphenyl-4-yl-pyrrol-1-yl)-
succinamic acid;

5 N-(1-Benzyl-2-methoxy-ethyl)-3-(3-biphenyl-4-yl-pyrrol-1-yl)-
succinamichydroxamic acid;

6-Biphenyl-4-yl-3(R)-2(S)-hydroxy-(1(S)-hydroxymethyl-2,2-
dimethyl-propylcarbamoyl)-hexanoic acid;

3-(1-Benzyl-2-hydroxy-ethylcarbamoyl)-5-methyl-hexanoic acid;

10 N¹-(1-benzyl-2-hydroxy-ethyl)-N⁴-hydroxy-2-isobutyl-
succinamide;

6-Biphenyl-4-yl-3(R)-2(S)-hydroxy-(1(S)-hydroxymethyl-2,2-
dimethyl-propylcarbamoyl)-hexanoic hydroxamic acid;

15 1-[4-Bromo-phenoxy)-benzenesulfonyl)-piperidine-2-carboxylic
acid;

6-Biphenyl-4-yl-3-(2-hydroxy-1-hydroxymethyl-propylcarbamoyl)-
hexanoic acid;

6-Biphenyl-4-yl-3-(R)-(2-oxo-cyclohexyl-1-(S)-carbamoyl)-
hexanoic acid;

20 6-Biphenyl-4-yl-3-(2-hydroxy-1-hydroxymethyl-propylcarbamoyl)-
hexanoichydroxamic acid;

2S-[(1S-Benzyl-2-hydroxyethylcarbamoyl)-3R-biphenyl-4-yl-
pyrrol-1-yl-methyl]-pentanoic acid;

25 3R-(3-Biphenyl-4-yl-pyrrol-1-yl)-N-(2R-hydroxy-cyclohexyl-1R-
yl)-succinamic acid;

2-(3-Biphenyl-4-yl-pyrrol-1-yl)-3-carboxamate-N-(1-hydroxy-3-
phenyl-prop-2-yl)-propionamide;

trans-2-(3-Biphenyl-4-yl-propyl)-cyclohexane carboxylic acid;

trans-2-(3-Biphenyl-4-yl-propyl)-cyclohexane carboxylic acid

30 hydroxyamide;

6-Biphenyl-4-yl-3-(R)-(1(S)-hydroxymethyl-2-(3-pyridyl)-
ethylcarbamoyl)-hexanoic acid;

N-(1-Benzyl-2-hydroxy-ethyl)-3-(4-biphenyl-4-yl-pyrazol-1-yl)-succinamic acid;

N-(8-Oxo-4-oxa-1,7-diaza-tricyclo[9.6.1.0^{12,17}]octadeca-11(18),12(17),13,15-tetraen-9R-yl)-3S-(3-phenyl-pyrrol-1-yl)-succinamic acid;

4-Acetyl-1-[4-phenoxy-benzenesulfonyl]-piperazine-2-carboxylic acid, N-hydroxyamide;

1-(Diphenylphosphinic)-piperidine-2-carboxylic acid hydroxamide;

3R-(3-Biphenyl-4-yl-pyrrol-1-yl)-N-[3S-(2RS-hydroxy-5-methyl)-hexyl]-succinamic acid;

N-(1-(S)-Benzyl-2-hydroxy-ethyl)-3-(R)-(2-biphenyl-4-yl-cyclopropylmethyl)-succinamic acid;

6-Biphenyl-4-yl-3-(R)-(2-oxo-1-tetrahydrofuran-3-(S)-ylcarbamoyl)-hexanehydroxamic acid;

1-[4-(4-Bromo-phenoxy)-benzenesulfonyl]-4-methyl-piperazine-2-carboxylic acid N-hydroxyamide;

4-(4-Methoxy-benzenesulfonyl)-thiomorpholine-3-carboxylic acidhydroxamide;

3-(Diphenylphosphinic)-propanoic acid;

3-(Diphenylphosphinic)-propanoic acid hydroxamide;

4-[2-(2-Carboxymethyl-5-(4-(3-hydroxy-propyl)-phenyl)-pentanoylamino)-4-methyl-pentanoylamino]-benzoic acid methyl ester;

1-[4-(4-Chlorophenoxy)benzenesulfonyl]-N-hydroxy-4-(N-methylcarbamoyl)piperazine-2-carboxamide;

4-[4-(4-Bromo-phenoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid N-hydroxyamide;

3-(3-Biphenyl-4-yl-pyrrol-1-yl)-N-(2,2-dimethyl-1-methylcarbamoyl-propyl)-succinamic acid;

1-[4-Phenoxy-benzenesulfonyl]-piperazine-2-carboxylic acid, N-hydroxyamide;

4[4-Phenoxy-benzenesulfonyl]-thiomorpholine-3-carboxylic acid N-hydroxyamide;

- 2(S,R)-{1S-Benzyl-2-hydroxyethylcarbamoyl-[3R-(4'-cyano-biphenyl-4-yl)-pyrrol-1-yl]-methyl}pentanoic acid;
- 2S-[3-(Biphenyl-4-yl)-pyrrol-1R-yl-(1S-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-methyl]-5-hydroxypentanoic acid;
- 5 1-(1,3-Dihydro-isoindeole-2-sulfonyl)-piperidine-2-carboxylic acid hydroxamide;
- 3-[3-(4'-Carbamoyl-biphenyl-4-yl)-pyrrol-1-yl)-N-(1-hydroxymethyl-2,2-dimethyl-propyl)-succinamic acid;
- 4-Methyl-1-(4-(4-chlorophenyl)benzenesulfonyl)-N-hydroxy-2R-piperazinecarboxamide hydrochloride;
- 10 1-[4-Chlorophenoxybenzenesulfonyl]-N-hydroxy-2R-piperazinecarboxamide;
- 2-(3-Phenyl-propylsulfonyl)-cyclohexane carboxylic acid hydroxamide;
- 15 1-(Pyrrolidine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;
- 1-(Piperidine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;
- 4-[4-Bromo-phenoxy-benzenesulfonyl]-oxothiomorpholine-3-carboxylic acid-N-hydroxyamide;
- 20 1-[4-(4-Methoxy-phenylsulfonyl)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;
- 1-[4-(4-Nitrile-phenoxy)-benzenesulfonyl]-4-(tert-butoxycarbonyl)-piperazine-2-carboxylic acid N-hydroxyamide;
- 25 2S-[3-(Biphenyl-4-yl)-pyrrol-1R-yl-(1S-hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-methyl]-pent-4-enoic acid;
- 6-Oxo-3-(4-phenoxy-benzenesulfonyl)-hexahydro-pyrimidine-4-carboxylic acid hydroxamate;
- 4-(t-Butoxycabonyl)-1-(4-(pyridin-2-yl)oxybenzensulfonyl)-N-hydroxy-piperazine-2-carboxamide;
- 30 4-[(4-Fluorophenoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid-N-hydroxyamide;

- N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-(3-phenyl-pyrrol-1-yl)-succinamic acid;
- 3R-(3-Biphenyl-4-yl)-N-(2-hydroxy-1S-hydroxymethyl-2-methyl-propyl)-succinamic acid;
- 5 1-(Pyrrolidine-1-carbonyl)-pyrrolidine-2(R)-carboxylic acid;
1-(Pyrrolidine-1-carbonyl)-pyrrolidine-2(R)-carboxylic acid
hydroxyamide;
- 1-Phenethylcarbamoyl-pyrrolidine-2(R)-carboxylic acid;
- R-4-[4-(Bromophenoxy)-benzenesulfonyl]-2,2-dimethyl-1-oxo-
10 thiomorpholine-3-carboxylic acid hydroxyamide;
- 4-(Ethoxycarbonyl)methyl-1-(4-(4-chlorophenyl)benzenesulfonyl)-
N-hydroxy-2R-piperazinecarboxamide hydrochloride;
- N-(2R-Hydroxy-indan-1R-yl)-3R-[3-(4-pyridin-4-yl-phenyl)-
pyrrol-1-yl]-succinamic acid;
- 15 N-(4,4-Dimethyl-2-oxo-tetrahydro-furan-3S-yl)-3R-[3-(4-pyridin-
4-yl-phenyl)-pyrrol-1-yl]-succinamic acid;
- N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-[3-(4-pyridin-4-
yl-phenyl-4-yl)-pyrrol-1-yl]-succinamic acid;
- 1-Phenethylcarbamoyl-pyrrolidine-2-(R)-carboxylic acid
20 hydroxyamide;
- N-(2,2-Dimethyl-1S-methyl carbamoyl-propyl)-3R-[3-(4-propyl-
phenyl)-pyrrol-1-yl]-succinamic acid;
- 1-(4-Benzyl-piperazine-1-sulfonyl)-piperidine-2-carboxylic acid
hydroxyamide;
- 25 3(S)-N-Hydroxy-4-(4-(pyridin-4-yl)oxybenzenesulfonyl)-2,2-
dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide;
- 2(R)-4-Methyl-1-(4-(4-fluorophenyl)benzenesulfonyl)-N-hydroxy-
piperazine-2-carboxamide;
- N-(2,2-Dimethyl-1-methylcarbamoyl-propyl)-3-(5-biphenyl-4-yl-
30 furan-2-yl)-succinamic acid;
- N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-(3-pyridin-4-yl-
pyrrol-1-yl)-succinamic acid;

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- 2-[4-(Pyridin-2-yl-oxy)-benzenesulfonylamino]-N-hydroxy-3,3-dimethyl butyramide;
- N-(4-Phenoxy-benzenesulfonyl)-3,3-dimethyl-S-(methylthio)-D-cysteine;
- 5 3-[3-(4'-Carbamoyl-biphenyl-4-yl)-pyrrol-1-yl]-N-(2,2-dimethyl-1-methylcarbamoyl-propyl)-succinamic acid;
- 3-[3-(4'-Cyano-biphenyl-4-yl)-pyrrol-1-yl]-N-(2,2-dimethyl-1-methylcarbamoyl-propyl)-succinamic acid;
- 2-(2-Biphenyl-4-yl-ethylsulfonyl)-cyclohex-1-ene-carboxylic acid
- 10 hydroxyamide;
- 6-(2-Biphenyl-4-yl-ethyl sulfonyl)-cyclohex-1-ene-carboxylic acid hydroxyamide;
- N-(4-Pyridin-4-yl-oxy-benzenesulfonyl)-3,3-dimethyl-S-(benzylthio)-D-cysteine;
- 15 3-[3-(4'-Carbamoyl-biphenyl-4-yl)-pyrrol-1-yl]-N-[2,2-dimethyl-1-(pyridin-4-yl-carbamoyl)-propyl]-succinamic acid;
- N-(4-Phenoxy-benzenesulfonyl)-3,3-dimethyl-S-(methylthio)-D-cysteine, N-hydroxyamide;
- 1-(4-Phenoxy-piperidine-1-sulfonyl)-piperidine-2-carboxylic acid
- 20 hydroxyamide;
- 3(R)-4-[4-(4-Bromo)phenoxybenzenesulfonyl]-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid;
- N-(4-[4-Chloro-phenoxy]-benzenesulfonyl)-3,3-dimethyl-S-(methylthio)-D-cysteine;
- 25 N-(4-[4-Chlorophenoxy]-benzenesulfonyl)-3,3-dimethyl-S-(methylthio)-D-cysteine, N-hydroxyamide;
- N-(4-[4-Chlorophenoxy]-benzenesulfonyl)-3,3-dimethyl-S-(methylsulfoxy)-D-cysteine, N-hydroxyamide;
- 2(R)-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-3-methyl-3-
- 30 (pyridin-2-ylsulfanyl)-butyric acid;
- 2(R)-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-3-methyl-3-(pyridin-3-ylsulfanyl)-butyric acid;

1-(4-Phenylsulfanyl-piperidine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;

1-[4-(4-Fluoro-phenoxy)-benzenesulfonyl]-3,3-dimethyl-5-oxo-piperazine-2-carboxylic acid;

5 N-(4-[4-Fluorophenoxy]-benzenesulfonylamino)-3-methyl-3-(1-benzyl-imidazole-2-yl-sulfanyl)-butyric acid;

2(R)-[4-(4-Fluoro-phenoxy)benzenesulfonylamino]-3-methyl-3-(pyridin-2-yl sulfanyl)-butyric acid, hydroxyamide;

10 3(R)-N-Hydroxy-4-(4-((pyridin-4-yl)methyl)oxybenzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide;

1-[4-(4-Chloro-phenoxy)-benzenesulfonyl]-4-(1-methyl-1H-imidazole-4-sulfonyl)-piperazine-2-carboxylic acid hydroxamide;

N-(2,2-Dimethyl-1S-methylcarbamoyl-propyl)-3R-[1-(4'-cyanobiphenyl-4-yl)-1H-pyrrol-3-yl]-succinamic acid;

15 3-Carboxymethylsulfanyl-2-(4-(4-fluoro-phenoxy)-benzenesulfonylamino)-3-methyl-butyric acid;

2,2-Dimethyl-1-oxo-4-[4-(pyridin-4yloxy)-benzenesulfonyl]-1S14-thiomorpholine-3-carboxylic acid hydroamide;

20 1-[4-(Pyridin-2-ylsulfanyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

2(R)-[4-(4-(fur-3-yl)-phenoxy)-benzenesulfonylamino]-3-methyl-3-(pyridin-yl-sulfanyl)-butyric acid;

2,2-Dimethyl-1-oxo-4-[4-(pyridin-4yloxy)-benzenesulfonyl]-1S14-thiomorpholine-3-carboxylic acid hydroamide;

25 {2-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-2-hydroxycarbamoyl-1,1-dimethyl-ethylsulfanyl}-acetic acid tert-butyl ester;

1-[4-(Pyridin-4-ylsulfanyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

30 2(R)-[4-(4-Bromo-phenoxy)benzenesulfonylamino]-3-methyl-3-(pyridin-yl-sulfanyl)-butyric acid, hydroxyamide;

trans-2-(2-Biphenyl-4-yl-ethylsulfanyl)-cyclohexanecarboxylic acid hydroxyamide;

- 2-[4-(4-Bromo-phenoxy)-benzenesulfonylamino]-N-hydroxy-3-methyl-3-(5-methyl-isoxazole-3-ylmethylsulfanyl)-butyramide;
- 2-[4-(4-Fluorophenoxy)-benzenesulfonylamino]-3-methyl-3-(carbomethoxyethylsulfanyl)-butyric acid;
- 5 1-[2-(Benzothiazol-2-ylsulfanyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;
- 3R-[3-(4-Cyano-phenyl)-pyrrol-1-yl]-N-(2,2-dimethyl-1S-methylcarbamoyl-propyl)-succinamic acid;
- 2-[4-(4-Fluorophenoxy)-benzenesulfonylamino]-3-methyl-3-(hydroxyethylsulfanyl)-butyric acid;
- 10 [4-Methoxy-benzenesulfonylamino]-3-methyl-3-(pyridin-2-yl-sulfanyl)-butyric acid;
- N-(4,4-Dimethyl-2-oxo-tetrahydro-furan-3S-yl)-3R-[1-(4'-cyanobiphenyl-4-yl)-1H-pyrrol-3-yl]-succinamic acid;
- 15 2-[4-(4-Fluorophenoxy)-benzenesulfonylamino]-3-methyl-3-(amidoethylsulfanyl)-butyric acid;
- [4-Methoxy-benzenesulfonylamino]-3-methyl-3-(pyridin-2-ylsulfanyl)-butyric acid;
- 2-[4-(4-Fluoro-phenoxy)-benzenesulfonylamino]-3,3-dimethyl-5-phenyl-pent-4-enoic acid;
- 20 5-[4-(4-Fluoro-phenoxy)-benzenesulfonyl]-4,5,6,7-tetrahydro-3H-imidazole[4,5,-c]pyridine-6-carboxylic acid hydroxyamide
- 2(R)-[4-(4-Methylphenoxy)benzenesulfonylamino]-3-methyl-3-(pyridin-yl-sulfonyl)butyric acid;
- 25 3(S)-4-(4-((Pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid;
- 1-[4-(Pyridin-4-ylsulfanyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;
- N-[1-(1H-imidazol-2-yl)-3-methyl-butyl]-3-[1-(4'-cyanobiphenyl-4-yl)-1H-pyrrol-3-yl]-succinamic acid;
- 30 3R-{3-[(4-Cyano-phenyl)-acetyl]-pyrrol-1-yl}-N-(2,2-dimethyl-1S-methylcarbamoyl-propyl)-succinamic acid;

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2R-[4-(4-Bromophenoxy)-benzenesulfonylamino]-3-hydroxy-3-methyl-butyric acid;

3(S)-2,2-Dimethyl-4-[4-(pyridin-4-ylsulfanyl)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid hydroxyamide;

5 2R-3-Methyl-3-[(5-methyl-isoxazol-3-yl)methylsulfanyl]-[4-(pyridin-4-yl-sulfanyl)-benzenesulfonylamino]-butyric acid;

2R-N-Hydroxy-3-methyl-3-[(5-methyl-isoxazol-3-yl)methylsulfanyl]-[4-(pyridin-4-yl-sulfanyl)-benzenesulfonylamino]-butyramide;

10 3,3-Dimethyl-2R-[4-(pyridin-4-ylsulfanyl)-piperidine-1-sulfonylamino]-butyric acid;

3,3-Dimethyl-N-hydroxy-2R-[4-(pyridin-4-ylsulfanyl)-piperidine-1-sulfonylamino]-butyramide;

15 2R-[4-(4-Bromophenoxy)-benzenesulfonylamino]-N-hydroxy-3-methyl-3-[(1-methyl-imidazol-2-yl)methylsulfanyl]-butyramide;

2R-[4-(4-Bromophenoxy)-benzenesulfonylamino]-3-methyl-3-[(1-methyl-imidazol-2-yl)methylsulfanyl]-butyric acid;

N-Hydroxy-2-[(4-methylbenzenesulfonyl)amino]acetamide;

20 1-[4-(4-Imidazol-1-yl-phenoxy)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

1-[4-(4-Imidazol-1-yl-phenylsulfanyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

2(R)-[4-(4-Chloro-benzoyl)-cyclohexanesulfonyl]-piperidine-1-carboxylic acid hydroxyamide;

25 1(R)-[4-(4-Chloro-benzoyl)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid amide;

1(R)-(4-Pyridin-2-yl-piperazine-1-sulfonyl)-piperidine-2-carboxylic acid hydroxyamide;

30 1(R)-[4-(4-Imidazol-1-yl-phenoxy)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid;

1(R)-[4-(4-Imidazol-1-yl-phenoxy)-piperidine-1-sulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

